In re: MIKE MOORE, ATTORNEY GENERAL ex rel. STATE OF MISSISSIPPI TOBACCO LITIGATION

IN THE CHANCERY COURT OF JACKSON COUNTY MISSISSIPPI
CAUSE NUMBER 94-1429

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The deposition of EDWARD GABRIELSON, M.D., was taken on Friday, November 15, 1996, commencing at 9:10 a.m., at the law offices of Goodell, DeVries, Leech & Gray, Twentieth Floor, One South Street, Baltimore, Maryland, before Deborah K. Wilkins, Notary Public.

APPEARANCES:

CHARLES W. PATRICK, JR., ESQUIRE
On behalf of Plaintiff

DONALD J. KEMNA, ESQUIRE
On behalf of Defendant Lorillard Corporation

Also Present: Gary W. Williams

Reported by: Deborah K. Wilkins, RPR

STIPULATIONS

It is stipulated and agreed by and between Counsel for the respective parties that the filing of this deposition with the Clerk of Court is hereby waived.

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WHEREUPON --

EDWARD GABRIELSON, M.D.,

a Witness, called for examination, having been first duly sworn, was examined and testified as follows:

EXAMINATION BY MR. KEMNA:

Q Dr. Gabrielson, we have introduced ourselves off the record, but I want to indicate to you that I represent Lorillard Tobacco Company in this matter, and I would like to ask you first of all to state your name and your office address for the record, please.

A My name is Edward Gabrielson. Office address is Johns Hopkins/Bayview Medical Center, 4940 Eastern Avenue, Baltimore, Maryland.

Q Doctor, I take it that you have had your

deposition taken before?

A Yes, sir.

Q I just want to mention up front that considering the subject matter that we may get into today, being that it certainly is a fairly technical area, I will ask you to listen closely to the questions. If the questions are not clear to you, somehow not understandable, just give me an indication, I will do my best to clarify the question, rephrase it, whatever is necessary for an understanding between us. Otherwise, if there's no indication from you, I will just assume that you understand the question and the answer to be responsive to the question.

Approximately how many times have you had your deposition taken, Dr. Gabrielson?

A I would estimate 20 or 30 times.

Q Would you list for me what types of cases you were deposed in?

A Most depositions have been related to asbestos litigation, either individual plaintiff cases

or insurance coverage litigation. I have also testified a few times as an expert for medical malpractice cases, and I have been deposed as an agent of our medical center in defense of a medical malpractice case. I have also been deposed one time because I witnessed a traffic accident.

Q How many times have you testified at trial?

A I have probably testified at trial, I would estimate, 20 times. Actually I should probably revise my estimate for depositions upward a little bit because I have been deposed more often than I have testified at trial.

Q So that if you were to move up your estimate of depositions by comparison to the number of times you testified at trial, would it be more than 20 to 30 as you have described?

A It would be more than 20 to 30. Probably 30 to 40.

Q Thirty to 40 times deposed.

The times that you have testified at trial, are they all the same types of cases that you have

described for testifying at deposition?

A Yes, sir.

Q So primarily asbestos litigation?

A Yes, sir.

Q And you have also testified at trial in medical malpractice matters?

A Yes, sir.

Q As to asbestos litigation, have you always served in the role of an expert witness in those cases?

A Yes, sir.

Q Has your role always been as an expert witness for the plaintiff in the litigation?

A In testimony, yes, sir, but I have prepared documents for defendants in asbestos litigation.

Q So you have served as a consultant?

A I have served as a consultant and prepared affidavits which were under oath, that were prepared and sworn under oath, used in some litigation.

Q For defense counsel?

A For defense counsel, yes, sir.

Q In litigation but not asbestos litigation, or was it asbestos litigation?

A It was asbestos litigation.

Q It was asbestos litigation.

To the best of your recollection, can you tell me what law firms you worked with who were plaintiffs' counsel in asbestos litigation?

A The majority of my work for plaintiffs' counsel in asbestos litigation has been for the Law Offices of Peter Angelos in Baltimore. I have also reviewed cases and testified for Peter Nicholl who is an attorney in Baltimore. I have reviewed cases for a firm in Maryland whose name I can't recall at the moment. I have reviewed cases and I have been deposed for Shepard Hoffman, who is an attorney in Baltimore. Those are the only set of firms that I can recall with regard to plaintiffs' suits for asbestos litigation.

Q Okay.

In those cases where you have served in a consulting role or have filled out an affidavit, can you recall who the defense counsel, what law firms you

worked with in those matters?

A There's a law firm in Baltimore, if I can go off the record for a few seconds and ask the court reporter to list the major law firms in Baltimore, I am sure I can recall the name.

Q Okay.

(Discussion off the record.)

BY MR. KEMNA:

Q Let's go back on the record.

A I prepared an affidavit for an attorney at the Semmes, Bowen & Semmes law firm who was defending a company in an asbestos litigation.

Q You have never then testified on behalf of the defense in asbestos litigation?

A No, sir, that case was settled. I was prepared to testify.

Q You mentioned some matters that involved insurance coverage. That was in the context of asbestos litigation?

A Yes, sir.

Q And in those matters, you were serving the

role as an expert on the plaintiffs' side in that litigation?

A Yes, sir. In those matters, I was representing the same companies that were the defendants in the original plaintiffs' suits.

Q In the medical malpractice matters that you participated, what types of medical malpractice, lawsuits, that is, what was the nature of the allegations in the lawsuits?

A I can recall two cases where individuals with asthma died and there were suits of wrongful death. I can recall a second case where a woman had a recurrent breast cancer, and she had claims against various physicians for inappropriate treatment.

Those are the cases that I can recall. It's been several years since I have participated in such a case.

Q Which party did you work with in those lawsuits?

A In each of those cases, I was working for the defense counsel.

Q And I take it you were serving the role of expert witness for defense counsel in those cases?

A Yes, sir.

Q Were those malpractice suits in the nature of a failure to diagnose the conditions involved, or were they otherwise involved with some type of inappropriate assessment of the patient's condition?

A I honestly couldn't tell you exactly what the plaintiff's allegations were, what the charges were and what they specifically said went wrong. My role was really limited to review of the medical records and whatever pathology materials were available, to testify as to the cause of death, the mechanism that led to the death, and that obviously had some impact on the case, although I really didn't get into depth as to how that specifically addressed the allegations.

Q Have you ever been involved in a lawsuit as a party to the litigation?

A I sued a man who built a house of mine, he didn't put in the right structure to hold up a center

beam, and I filed that case myself.

Q So you handled it on your own without counsel?

A Yes, sir.

Q It was a lawsuit against a builder?

A Yes, sir.

Q Any other matters?

A No, sir.

Q You have never been a defendant in a malpractice lawsuit?

A No, sir.

There's some currently pending litigation that has named another physician at the Johns Hopkins/Bayview Medical Center and has also named the medical center as defendants, that's a pending malpractice case. I have been deposed and will probably be called to testify as an agent for the hospital because the hospital is being sued for something with regard to the clinical laboratory testing, and I am the director of the clinical laboratories, but I have not personally been named as

a defendant in a malpractice suit.

Q Doctor, I had an opportunity to look at your curriculum vitae, and I made note of the fact that you had done your residency at the University of Colorado. In that pathology department, can you recall the names of individuals who were members of the pathology department at the time that you were in your residency?

A The chair of the pathology department was Dr. Pierce, G. Barry Pierce. Other faculty included a Dr. Fennell, Dr. Firminger, Dr. Sykes and Dr. Ericson, Dr. Spears, Dr. Fink.

I apologize, because I can recall faces and almost get the name right, but I will try very hard to remember the names of these faculty people.

Dr. Gordon, Jules Gordon, Dr. Clark, Dr. Guggenheim, Dr. Sanford, Dr. Warren, Dr. Winters.

These are all the names that I can recall now on the faculty at University of Colorado, department of pathology.

Q Is the Lung Cancer Institute of Colorado a

part of the University of Colorado?

A I don't know exactly what the Lung Cancer Institute of Colorado is. I know that there's a very active research program in lung cancer at the University of Colorado that is directed by Paul Bunn. Dr. Bunn is the head of oncology at the University of Colorado, is director of this program. They have a lung cancer SPORE grant from the NIH, and we have active interactions with them. Dr. Bunn was not on faculty at the University of Colorado at the time I did a residency there.

Q The SPORE grant that you refer to is the same grant source from NIH that you have listed in your curriculum vitae; is that correct?

A Yes, sir.

Q So that as part of that program, you have ongoing collaboration with the group in the pathology department from the University of Colorado?

A Yes, sir. The pathologist at the University of Colorado who is most active in the SPORE program is Wilbur Franklin. Dr. Franklin was not at

the University of Colorado when I was a resident, so I have met him since I have come to Johns Hopkins.

MR. KEMNA: Have this marked as Deposition Exhibit 1, please.

(Defendants' Deposition Exhibit No. 1 was marked for identification.)

BY MR. KEMNA:

Q Doctor, I am going to show you what's been marked as Deposition Exhibit 1, it is entitled Defendants' Notice of Deposition: Dr. Edward W. Gabrielson.

Did you receive a copy of that notice in advance of this deposition, Doctor?

A Yes, sir. I have a copy with me. It appears to be basically the same document.

Q Did you take note of the requests for production of documents that occurs under paragraphs 1 and 2 of Deposition Exhibit 1?

A Yes, sir.

Q Have you produced documents in compliance with those requests?

A I believe so. I discussed this with Mr. Patrick, I believe it was yesterday or two days ago. It is impossible for me to bring all documents upon which I will rely for my testimony because I really can't anticipate exactly what my testimony will be.

I also have ongoing research that is not yet publicly available. I discussed this with Mr. Patrick. What we have decided is that I would not rely upon any of that work until it is published and therefore publicly available, and I would make every effort to make that available to defense as soon as the work is accepted for publication.

MR. PATRICK: Let me just make a brief statement for the record.

It is my understanding that this issue about the documents to be produced and the items to be produced that have been identified in the notice of deposition is still before the court, and, as we have discussed in prior depositions, the position of the plaintiff is that we will comply with the order of the court, when it is made, regarding the production of

materials, and if it becomes necessary we will reconvene the deposition of Dr. Gabrielson if the court deems that necessary.

Dr. Gabrielson did bring with him today a folder of medical articles that he may find helpful with his testimony, but as far as the notice is concerned, we did not produce all of the materials on which he relies at the date stated in the notice, and Dr. Gabrielson did not comply because it was at my direction that he did not comply.

BY MR. KEMNA:

Q Doctor, the folder of materials that you have with you today, then, is to the best of your estimation documents that would fall within the requests stated on the notice of deposition but not all the documents that were requested; is that accurate?

A Yes, sir. What I have attempted to do was to select articles that I would be very likely asked to discuss but that have not been introduced or discussed by other experts. For example, there's a

great deal of general information on the health effects of tobacco in the Surgeon General's reports and other medical literature, but it is my understanding that there are other experts that will be testifying as to this material.

I have tried to limit what I have brought today to an area that I am not aware of any other expert for the plaintiff testifying on.

Q Is it your intent by the scope of the materials that you are producing here today to be only those materials that fall within the scope of your particular expertise for which you are offering testimony in this case?

A I don't know what I will be asked to offer testimony on. My expertise is as a pathologist and practicing physician, with a particular emphasis on cancer, carcinogenesis and molecular biology of cancer. The articles that I have brought with me are articles that discuss molecular biology and carcinogenesis of lung cancer.

As I said, I am a general pathologist. I

teach medical students about lung disease, other diseases. I have, I think, a professional level of knowledge of those areas. I don't know if I will be asked to testify in those areas, but it is my understanding that Mr. Patrick's firm has other experts that will cover those areas, and I am not the primary person to discuss those other areas.

Q In the materials that you have produced today, are there any documents that are correspondence with plaintiffs' counsel in this case or otherwise documents that they provided to you in advance of the deposition?

A No, sir. I do not believe that I have corresponded to Mr. Patrick's firm in writing at all regarding this case. Our contacts have been relatively brief.

Mr. Patrick's firm sent to me, I believe it arrived yesterday, a copy of a deposition that was taken of Victor Roggli several days ago. Mr. Patrick thought that that would help me get a flavor of what the deposition would be like. They also sent to me

some copies of the Surgeon General's reports from 1980 to 1989, around that time, that was at my request because I had seen those reports years ago, I had not saved them, and when I went to the library at our hospital I found that they did not have them, and I asked his law office to send those to me. I received them yesterday, and I really haven't had time to look at them in advance.

Other than that, there's really been no written correspondence between myself and Mr. Patrick's firm.

Q They haven't provided you with any other documents?

A Several months ago, maybe as long as one year ago, I received some articles on -- they were original articles on family linkage of difficulty in smoking cessation, and I was asked to review articles and send back some comments, and actually I never did because I just simply didn't have the time, and I didn't really have any other correspondence with Mr. Patrick's firm with regard to that matter.

Other than that, I have not received any written documents from his firm, and, as I said, I have not written back to them.

Q Do you still have the articles that were sent to you regarding some type of problem with cessation of smoking?

A I am sure I don't. Between the time that I received those articles and the present time, my office moved, and I just simply left many things behind. I am sure that that was one of the things that I left behind.

Q You have mentioned Mr. Patrick's firm. Have you had contact with any other law firm representing the plaintiffs in this action?

A No, sir.

Q Have you discussed this lawsuit with anyone other than Mr. Patrick or members of his law firm?

A I told my wife what I am doing. My mother knows. The chief of the service at Johns Hopkins/Bayview knows where I am today.

At Johns Hopkins we are required to

disclose outside activities. In the latter part of June or early July when I provided my written disclosure of what I would be doing for this year, I informed my chairman that I would be involved in some litigation. I really didn't know what the particulars would be, but I listed it as one of my anticipated outside activities.

I don't really recall having discussed it with other people. In particular I have not discussed it with professional colleagues.

I would make one exception to that. I think that Dr. Abeloff, Martin Abeloff, who is chairman of oncology at Johns Hopkins, also is aware that I am here because I discussed it with him.

Q Beyond discussing the fact of your involvement in the case, have you discussed the substance of any of the allegations in the lawsuit or otherwise your opinions that you would expect to give in this case?

A No, sir.

In fact, I think I have a rather vague

understanding of what the allegations in the lawsuit are and of what the plaintiff is seeking in the lawsuit, but I haven't really discussed that with anybody other than the personal contacts that I have told you.

Q Are you personally acquainted with any of the other experts that have been listed by the plaintiff in this case?

A I have not seen a listing of other experts. I am aware that Dr. Roggli will testify, I have met Dr. Roggli a couple of times, and I do not know who the other experts will be.

Q And you have not discussed this case with Dr. Roggli?

A No, I have not.

Q When was the first time that you were contacted regarding your participation in this lawsuit?

A I would estimate that it was about one year ago, maybe a little earlier, and I was contacted by Ann Ritter, I believe that is, I believe that is her

name, who is an attorney at Mr. Patrick's firm.

Q Between that initial contact with Ms. Ritter and today, how many times have you talked to anyone representing the plaintiffs in this case, in that period?

A I can go through the whole history.

Ms. Ritter contacted me first by phone, then came to my office and talked to me for about one hour, maybe it was a half, one-half hour, and that was perhaps a year or a year and a half ago.

Some months after that I received this article asking me to read it and send back some comments, which I failed to do, and then there was actually quite a long hiatus where I did not have any contact with the law firm.

Several months ago I was contacted by Deana Campbell, who is -- I would guess that she is a paralegal or some assistant at the law firm of Mr. Patrick, and she asked me to set aside some time for deposition. I was unaware that the litigation was proceeding or that I would be involved in the

litigation. So we scheduled some time.

Q Let me interrupt you for just a moment.

When were you contacted by Deana Campbell; do you recall?

A This is going to be a guess, but I would think that it was two or three months ago. Perhaps two months ago.

Q So at that point in time when you talked to Deana Campbell, did you realize that you were going to be listed as an expert in this case?

A Yes, sir. Then I realized that the litigation was proceeding and that I would be listed as an expert in the case.

Q Did you have any discussion about the nature of your testimony that you would be expected to give in this case?

A I did when Ann Ritter first met with me. I did not really discuss that with Deana Campbell.

I may have asked her something to the effect about what would my testimony be. She told me that Charles would be contacting me and talking to me

about that.

Q Okay.

As to your discussion with Ann Ritter at the outset, what were you told regarding the scope of your opinions to be given in this case?

A Well, it was my understanding that the plaintiffs in this case wanted to educate the jury with regard to the multiple steps of carcinogenesis, give the jury some background with regard to the number of mutations that are required for cancers to develop, what are the types of mutations that are involved in cancers, and use this to build an overall model of how cancers develop.

Q Anything else that was discussed with you that would fall within the scope of your opinions on this case?

A Not really. It was my understanding at that time, and it remains my understanding, that there are a number of other expert witnesses involved that will discuss areas which include epidemiology, perhaps chemical composition of cigarette smoke, addiction, a

number of other topics.

Q But the areas such as epidemiology are not areas that you expect to express expert opinions on in this case; is that correct?

A I don't expect to express any depth of expert opinions on. I have read epidemiological studies, I think I have some understanding, but this is not something that I personally do. I am not familiar with all the epidemiologic studies, and I don't expect to discuss them to any depth.

Q And the same question with respect to chemicals or constituents of tobacco smoke. You don't expect to express expert opinions with respect to the chemical composition of tobacco smoke; is that correct?

A I have somewhat more familiarity with this area than I do with epidemiology because I have been involved in in vitro carcinogenesis experiments where I have used different components that are components of tobacco smoke.

Again, I don't anticipate that I will be

called on to discuss this in great depth with regard to the chemical nature of tobacco smoke, but I really can't say for sure what is expected of me.

Q Is it fair to say that your understanding of your expert testimony is that it will be limited to the subject matter that would be generally under the category of lung cancer?

A That was my original understanding, although when I talked to Mr. Patrick the other day about what I would be expected to testify on, he indicated that there are a number of other diseases that are involved in this litigation and I may be asked to comment on, for example, molecular mechanisms of emphysema development. I myself have not done research in this area, but I have some familiarity with the literature.

I expect that the great majority of my testimony will be related to cancer development, probably more lung cancer than other types of cancers, but, in general, cancer development.

Q Now, we are going through the chronology of

contacts that you have had with plaintiffs' counsel in advance of the deposition, and we left off with your discussion with Deana Campbell.

How long did your discussion with Deana Campbell last?

A I haven't really discussed any of the topics in depth with Ms. Campbell, and because we had no depth to the conversations, that is why I have concluded that she's a paralegal or assistant rather than one of the attorneys. She kept telling me that I would be contacted by Mr. Patrick and that he would discuss this more in detail with me.

I had several contacts with Ms. Campbell for scheduling this deposition, and then I think I had my first conversation with Mr. Patrick perhaps two or three days ago. Actually I recall we had a scheduled telephone conversation on Monday at 12 o'clock or 1 o'clock.

Q That's Monday, this week?

A Yes, sir.

Q Your first contact with Mr. Patrick, was

that a telephone conversation then?

A Yes, sir.

Q How long did that last?

A It was between a half-hour and one hour.

Q What was discussed during the course of that conversation?

A He gave me some background with regard to the scope of this litigation, the purpose of it. He gave me some background as to how they are structuring the case and the involvement of multiple expert witnesses. He discussed with me what my role would be in the case with respect to all the other expert witnesses that are involved. He discussed with me the request to bring records.

I expressed some of my concerns about not being able to bring with me an entire library or not being able to bring with me data of work that's in progress, and we discussed what I should bring, what types of things he would anticipate my testimony being focused on.

Q When did you first see the notice of

deposition, Deposition Exhibit 1?

A It was faxed to me a week, possibly read that -- it appears to be October 1st of '96.

MR. PATRICK: That is the notice.

A I was contacted, I would guess, a month and a half ago, perhaps the date was set, and then this notice was faxed to me.

Well, I'm sorry. Here it says October 16th.

Q Doctor, that's a file stamp date.

A But it could not have been faxed to me before that file stamp date; is that correct?

Q That should be the case, yes.

A So it was probably around October 17th that this was all sent to me.

In fact, when I look at this, it appears that this fax was sent to the Ness, Motley law firm, they put that in the package with this letter and sent it to me on October 17th, so that would be about a month ago that I received this.

Q When you received this from the Ness,

Motley firm, did you look at the notice and make note of the date for production of documents in that notice?

A Yes, sir.

Q All right.

Did you discuss with anyone the necessity for complying with the date indicated in the notice for production?

A I probably discussed that with Ms. Campbell, and she said somebody from the law firm would be contacting me.

When I looked at it, I just thought that would be impossible to provide it, everything.

Q No one contacted you from Mr. Patrick's law firm in advance of the date that you had the telephone conversation, that would be Monday this week; is that correct?

A Other than Ms. Campbell.

Q And she gave you no direction on that but to indicate that someone else would be talking to you about it; is that correct?

A Yes, sir.

Q Now, in your conversation with Mr. Patrick this week when he discussed with you what would be expected to be within the scope of your expert opinions, can you recall to the best of your recollection what he told you?

A I cannot recall the verbiage he used. I can only recall the meaning that I took away from the conversation.

It's my understanding that he wanted me to be able to talk about the molecular genetics of lung cancer, molecular carcinogenesis, what is known with regard to tobacco injury to epithelium and how it is involved in the carcinogenesis process. But it was really my understanding that I was here mostly to talk about molecular and cellular carcinogenesis.

Q Anything else you can recall?

A There are things that I asked him about, and it was my recollection that specifically I am not being asked to be an expert and discussing in any great depth animal experiments that have been done

over the years, I am not being asked to discuss in any depth the epidemiology of cancer, the epidemiology of other diseases.

When we talked about other diseases caused by tobacco, the only thing that I do recall being outside of the cancer arena that he appeared interested in having me possibly discuss would be molecular injury leading to emphysema. That is basically what I remember from the conversation.

Q You say that conversation lasted for somewhere between a half an hour and an hour?

A Yes, sir.

Q Any other discussions with Mr. Patrick or anyone else representing the plaintiffs in this case?

A No, sir. The only other discussion that I have had with plaintiff counsel was, I met Mr. Patrick for breakfast this morning slightly after 8 o'clock, and he basically reiterated what we talked about on the telephone.

Q Nothing new this morning in your conversation beyond the discussion that you had on

Monday this week?

A Well, he told me that his wife works part-time because he travels a lot.

Q Nothing relating to the substance of this case?

A That is correct. In fact, in the time that I met with him, we probably talked about the substance of this case for ten or 15 minutes at the most.

Q Did you read the deposition of Dr. Roggli in advance of this deposition today?

A I had available only about 10 minutes or so to peruse that deposition. It was faxed to me sometime yesterday. I saw it shortly before I went home, and I took it home with me, but I had other matters to deal with.

Q Throughout this time that you had contact with plaintiffs' counsel, and this would be as I understand it Mr. Patrick's firm, and also if I understand correctly the first time would have been approximately a year to a year and a half ago with Ms. Ritter; is that correct?

A Yes, sir.

Q Throughout this time period from that first conversation regarding the case to your last conversation with Mr. Patrick in advance of this deposition, did you discuss the contents of any report that would outline your opinions in this case?

A No, sir. I have not been asked to prepare a report or any type of written document. I have really not been asked to prepare anything specifically for this case.

Q Have you seen any document that purports to be a description of your expert testimony to be offered in this case?

A I have. This was sent to me (indicating). I believe that was sent at about the time that the deposition was being scheduled. That was sent by Ms. Campbell.

Q Can you recall approximately when you received this document?

A I am going to guess two or three months ago at about the time that Ms. Campbell was trying to find

out when I would be available for deposition.

MR. KEMNA: Let's have this document marked as Deposition Exhibit 2.

(Defendants' Deposition Exhibit No. 2 was marked for identification.)

BY MR. KEMNA:

Q The document just marked as Deposition Exhibit 2 is entitled Subject Matter and Substance of Anticipated Testimony with an indication in the upper left-hand corner that it is regarding Dr. Edward W. Gabrielson.

That is correct, isn't it, Doctor?

A Yes, sir.

Q Doctor, did you participate at all in the drafting of this document, Deposition Exhibit No. 2?

A It was sent to me and asked me if it met my approval. I did not draft it myself.

Q Okay.

Did you respond to Mr. Patrick's firm in any way after receiving a copy of this document?

A I told whoever called me, and I believe it

was Ms. Campbell, that this met my approval.

Q Doctor, are you serving in a capacity as an expert on the causation of lung cancer in this case?

A I probably don't understand the exact meaning of the question. As far as causation of lung cancer is concerned, it is my opinion that cigarette smoking causes lung cancer. I don't know that my testimony is necessarily intended to prove that, although the investigations that I expect to talk about certainly do provide additional evidence.

I think what I am going to be talking about already is built on the common understanding in the scientific community that tobacco smoke causes lung cancer. I don't think that this work was done in an attempt to determine whether or not cigarette smoke causes lung cancer. I think that that was already a given for this type of work. This work was done to understand mechanisms. However, that is my understanding of it. I think you would have to ask Mr. Patrick what exactly his intent is with regard to my testimony, how it fits into the overall scheme.

Q Well, let's go at this in a slightly different direction, Doctor.

You consider yourself to be an expert in the field of carcinogenesis research; is that correct?

A Yes, sir.

Q You consider yourself to be an expert in the field of smoking and health?

A Yes, sir.

Q Is your opinion regarding cigarette smoking as a cause of lung cancer simply a personal opinion of yours or is it an opinion that you are expressing as an expert in the causation of lung cancer?

A Both.

Q So you consider yourself to be an expert in the causation of lung cancer?

A Yes, sir.

Q And your opinion regarding smoking is more than simply the fact that you have read about smoking and its association with lung cancer?

A Well, it's based on all of my reading. It's based on work that I myself have done, it's based

on my clinical observations, and I guess you would also say it is based on observations that I make personally, but from the perspective of being a physician.

Q Is it a focus of your research to explore whether or not cigarette smoking is a cause of lung cancer?

A No, sir, I don't think that that is the focus of anybody's research now. That's accepted universally by the scientific community. The focus of research now is to understand mechanisms of carcinogenesis. I don't think anybody will test the hypothesis that cigarette smoke causes cancer; that is, I think it's been demonstrated beyond any reasonable doubt from a scientific standpoint.

What scientists are investigating now is how it causes cancer, what are the early changes in the development of this cancer, the critical issues are how we can slow down or stop the development of cancers, how we can know more about the cancers so we can treat them. At least those are the goals from my

perspective.

I think that other people are trying to prevent the cancers by getting people to stop smoking or not start smoking, but again, I don't think that anybody in the scientific community now would consider cigarette smoking as a cause of cancer at the hypothesis level, I think that has been demonstrated beyond any reasonable doubt.

Q So it's the mechanisms of carcinogenesis that can be described as at the hypothesis level at this time?

A Yes, sir. And with regard to that, a lot of progress has been made and what was at a hypothesis level five or ten years ago I think has also now been established to a reasonable degree of certainty. We are moving further and further into the mechanisms, but as we are moving deeper and deeper into understanding the mechanisms, that is where the level of the hypotheses are at this time.

Q And so it is fair to say, Doctor, that there is a need for further research to really have an

understanding of the entire chain of events that would be regarded as the mechanism for the causation of cancer?

A Well, there are specific areas that I think should be a focus of research attention, and again research should be directed so that the outcome will have meaning. The goals of carcinogenesis research should be able to identify potential targets for prevention. But these are the areas that I think are deserving of more research. Nobody would get peer review funding to test the hypothesis of whether or not cigarette smoking causes lung cancer because that has been demonstrated beyond any reasonable doubt. The money, the energy is better spent at a different level right now.

Q So you really haven't spent any considerable time yourself examining the literature that relates to an association between cigarette smoking and lung cancer because you believe that to be already established. Is that fair?

A Well, I think early in my training I was

required to review some of the epidemiologic literature, for example, British physician studies. I have reviewed ongoing epidemiologic literature with regard to smoking cessation and cancer. I have reviewed some of the animal experimental data. That's not something that I have looked at in the past several years, and that's not an area that I consider to be where I really focused my attention.

I have accepted myself that smoking is a cause of cancer. I do that based on the literature that I have reviewed and my own personal observations as well as the current data that continues to add more and more support to that.

MR. KEMNA: Let's have this document marked as Deposition Exhibit 3.

(Defendants' Deposition Exhibit No. 3 was marked for identification.)

BY MR. KEMNA:

Q Just for the record, I have marked as Deposition Exhibit 3 the Defendants' Notice of Deposition that actually came from Dr. Gabrielson's

file indicating the date of faxing of the document to Dr. Gabrielson that he testified to.

Let's go off the record for a moment.

(A short break was taken.)

BY MR. KEMNA:

Q Doctor, how many of your publications would you say relates to the subject of the causation of lung cancer?

A Would I be allowed to look at my CV and go through that?

Q Sure.

A I had a copy somewhere.

Specifically related to causation of lung cancer?

Q Yes.

A I am going to estimate about ten of the publications have at least some major content that deals with causation of lung cancer.

Q Is it fair to say that more specifically those publications, the ten that you mentioned, would be exploring the mechanisms of carcinogenesis for lung

cancer?

A Yes, sir.

Q What's the most recent publication you have that explores the mechanisms of lung cancer causation?

A I don't know exactly how to answer that. I have publications that deal with molecular changes in lung cancers, that is certainly part of lung cancer development or the carcinogenesis process, but those publications have not dealt with specific agents or how agents cause these genetic alterations.

Are you asking what papers deal specifically with molecular or cellular damage caused by agents that cause lung cancer?

Q Yes, let's go with that description.

A The most recent paper I recognize is one that was published in 1994 regarding oxidant stress responses in mesothelial cells that were exposed to asbestos. I think that is what you asked me originally, what was my most recent publication.

Q As you have indicated before, Doctor, this research is geared to understanding what type of

molecular mechanisms may be at play in the development of cancer. Is that a fair description?

A Yes, sir.

Q And while some of the agents that you may have in mind during the course of this research, you believe there would be little question regarding whether or not they caused the disease process, those agents are used in the process of attempting to explore what the precise molecular mechanisms may be that bring about the disease of cancer. Would that be accurate?

A I think I understood your question, and I would agree that yes, these investigations were basically directed at understanding molecular mechanisms.

Q By virtue of the fact that there's a good deal of ongoing research in this area of molecular mechanisms of carcinogenesis, there's much that is yet to be understood about the precise molecular mechanisms of carcinogenesis; is that correct?

A There still is a great deal for us to learn

regarding molecular mechanisms, yes.

Q What medical or scientific texts do you consult on somewhat of a regular or maybe semi-regular basis?

A With regard to a lung disease or with regard to my practice of pathology?

Q Let's start with respect to pulmonary pathology generally.

A I think that there's a textbook by Dr. Thurlbeck on lung pathology that is particularly useful, and I refer to that on a regular basis for non-neoplastic diseases of the lung. Dr. Spencer also has an excellent textbook on lung pathology which I refer to for discussions on non-neoplastic diseases of the lung.

Textbooks that deal with cancers of the lung from a pathologist's standpoint would include the Armed Forces Institutes of Pathology Fasicles, tumors of the lung and tumors of the serosal surfaces. I think those fasicles are excellent, and those I would consider to be my references of choice for cancers of

the lung. Pathology of cancers of the lung.

As far as textbooks for molecular carcinogenesis, I don't really think there are any. This is a field that is moving fast enough that it doesn't really allow for textbooks to be written and be timely by the time they are published.

Q Any other textbooks that come to mind regarding lung cancer -- or excuse me, pulmonary pathology?

A These are the books that I have available to me within the department or on my shelf, and these are the ones that I use on a regular basis.

Q All of the texts that you have mentioned under the heading of pulmonary pathology and then more specifically cancers of the lung, are these texts that you would consider to be authoritative in your field?

A Authoritative is a word that lawyers like to use. I can regard a textbook as being excellent in general and find specific issues that the textbook addresses where I think that they have made a misstatement or some erroneous statement.

I think in general these textbooks are excellent. I cannot off the top of my head find anything wrong with the way Dr. Thurlbeck discusses non-neoplastic diseases of the lung. I can't off the top of my head think of anything wrong with the way the Fasicles discuss cancers of the lung. I may find some specific issue that I would disagree with them on, but I can't think of any such issues at the time.

Q Are you familiar with Dail & Hammer's text on pathology?

A Dail & Hammer, yes, that is also a very good textbook for lung pathology.

Q Is that one that you would put in the same category with the other texts that you have just mentioned?

A Yes, sir. I am not as familiar with that book as I am Dr. Thurlbeck's book, but from what I have seen of the text by Dail & Hammer, it is an excellent text, very comprehensive, and I hold it in high regard.

Q Are you familiar with DeVita's text on

cancer, Principles and Practice of Oncology?

A Yes, sir. The textbook that was edited by Dr. DeVita and Dr. Rosenberg on oncology practice, yes, sir, I have read portions of that, and I think that that's also a very good textbook.

Q What medical journals do you review on a regular basis?

A I review Science, New England Journal of Medicine, Cancer Research, Nature Medicine, Nature Genetics, Nature on a more or less regular basis in that I will pick up most issues that come out and at least look through the index and read some selected articles.

Other journals, I will usually read articles only after doing some type of search and finding a topic of interest.

Q The journals that you have listed, would you be able to put them in a category similar to the way you have described the texts that you have listed and that you could characterize them as good, fair, excellent, whatever characterization you might have?

A They are all highly-regarded journals, and in general I regard the journals and their editorial policies highly. I have seen articles in each of those journals that I feel are -- or I have felt were not great articles that maybe should not have been published in such a prestigious journal, but I think in general that the editorial policies, the reviewer, the editorial boards of these journals are good, they do their job, they do good articles, and most of what comes in those journals is good science.

Q These are journals that would be considered peer reviewed publications; is that correct?

A Yes, sir.

Q Have you ever, besides your participation in litigation through testimony, have you ever made any public statements regarding cigarette smoking and the causation of disease?

A I don't think I have made any statements that you would regard as public statement. It's impossible to give a lecture to medical students on lung disease without discussing cigarette smoke and

the health effects of cigarette smoke. I don't regard a lecture to medical students as a public statement, it is rather private, and they pay the university money for the privilege of hearing about the pathology of lung disease. I have never really made any general public statement with regard to smoking and lung disease or smoking and cancer.

Q Do you prepare course materials for distribution to medical students or any students that may be a part of classes that you teach?

A Yes, sir, I have. I have prepared such materials.

Q Within those materials that are prepared, have you included information that relates to cigarette smoking and disease?

A Yes, sir.

Q Do you currently have in your own personal files or accessible to you those course materials that would include those statements?

A I probably do. My current lecture responsibilities at Johns Hopkins are less than they

have been in previous years. Previously at Johns Hopkins, and at the University of Maryland, I would lecture medical students on obstructive lung disease and lung cancer, and I believe I still have my lecture outlines for those topics.

Q What medical text or maybe even assigned course textbooks are used when you teach students regarding pulmonary pathology?

A Primarily the pathology text by Dr. Robbins, Stanley Robbins. I believe the title of it is the Pathologic Basis of Disease. That is the textbook that I believe is used by the vast majority of medical schools in the United States.

There is one other textbook that was used, I believe at the University of Maryland, for one or two years by Dr. Farber, and I forgot the title of it, but it is again a general textbook for pathology.

Q Do you consider that those texts were the appropriate source of information for the use of students in your courses on pathology?

A Yes, sir, I do. I thought that they were

both very good textbooks.

Q Have you ever been involved with any organizations that have as at least part of their focus discouraging cigarette smoking in society?

A Yes, sir. I am a member of the American Association for Cancer Research; they take a very strong position on smoking and cancer. I have been a member of the American Thoracic Society. The American Thoracic Society also takes a very strong position on smoking. I am a member of the American College of Pathologists, the United States and Canadian Academy of Pathology. I am not aware of these societies having any positions on smoking, although it is possible that they do. Those positions certainly have not been as visible as have the positions of the American Association for Cancer Research and the American Thoracic Society.

Q Do you participate in any way with the American Cancer Society?

A Not directly. I have had research support from the American Cancer Society. In fact, I am now

an investigator on a grant for breast cancer research from the American Cancer Society. I don't participate directly with their everyday activities.

Q Are there any other organizations such as Stop Teenage Addiction to Tobacco or any other types of organizations that tend to be lobbying organizations or public information organizations regarding cigarette smoking that you have been affiliated with?

A No, sir.

Q What is your current faculty appointment at Johns Hopkins?

A I am an associate professor of pathology and oncology.

Q How long have you been in the position of associate professor?

A I believe it's two or three years.

Q Before that you were an assistant professor?

A Yes, sir.

Q Do you have any affiliation with any other

teaching institution?

A I have an appointment at the University of Maryland School of Medicine.

Q What is that appointment?

A I am not sure. I believe I am still a research assistant professor at the University of Maryland.

Q Do you have any ongoing teaching responsibilities at the University of Maryland?

A No, sir. I have not taught at the University of Maryland in the past, I believe, two or three years.

Q So that appointment is really of marginal importance in terms of the amount of time it might take from your professional practice --

A At this time, yes.

Q -- that you participate.

Doctor, have you ever smoked?

A I didn't know you were going to get personal here.

When I was 16 years old I think I probably

smoked two or three cigarettes or portions of two or three cigarettes.

Q Any smoking after that point in time?

A When I was in college, playing poker sometimes, we all had cigars.

Q Do you currently smoke at all? Cigars? Cigarettes?

A No, sir.

Q Do any friends or family members smoke?

A I know of a number of people that I would consider to be friends that smoke.

Q If those friends come to your home, do you permit them to smoke in your home?

A No, sir.

Q Do you make any recommendation to your friends who smoke regarding their smoking behavior?

A I nag them all the time.

Q How do they respond?

A Well, unfortunately they agree that it's bad for them, but they just don't seem to recognize that those adverse health effects are going to come

about at some point. I think that they just think it's in the future, they will deal with the problem later.

Q Doctor, we have talked a bit about your area of expertise, and I'm going to go through a series of questions, and I will apologize in advance if they seem a bit tedious, but it won't take very long.

At the outset, of course, your field of specialty in medicine is pathology; is that correct?

A Yes, sir.

Q So within that field you would consider yourself to have expertise; is that correct?

A Yes, sir.

Q Now, with respect to pharmacology, would you consider yourself to have expertise in pharmacology?

A Not to a great depth of expertise.

Q Would you consider yourself to have any expertise in the field of psychopharmacology?

A Again, that is not an area that I have

expertise to any great depth on.

Q Any expertise with respect to dependencies or addictions?

A That is an area that I don't have a great depth of expertise.

Q I take it you would not consider yourself to be an expert in the field of oncology?

A I don't treat patients for neoplastic disease, and my understanding of treatment of patients comes mainly from the interactions that I have with practicing oncologists.

As a pathologist, I am a very important part in the diagnosis of neoplastic diseases. I work closely with practicing oncologists that treat the patients to discuss natural history of the disease, prognosis of the disease, likelihood of a particular tumor to respond to therapy. I do have an expertise in the overall field of oncology with an emphasis on the diagnosis of disease and an understanding of the biology and behavior of cancers.

Q So it is fair to say that if you were to

look at the aspect of oncology that relates to treatment of patients, that's where you would not feel that you had expertise?

A I can maybe be more specific.

If I diagnose a cancer such as a lung cancer or a breast cancer, I would discuss with the treating physician not only that I have a diagnosis but certain features of the cancer, the extent of the cancer, the stage of the cancer, the apparent biological behavior of the cancer, and I would discuss with the treating oncologists what types of treatments are likely warranted. For example, do I believe that the cancer is not aggressive and surgery is the only treatment needed, or would I believe that a particular tumor is likely to be radiosensitive because of the rate of cell division.

We perform receptor studies on breast cancers to make -- which ultimately lead to recommendations as far as whether or not a breast cancer would be treated by hormone therapy. But as far as the scheduling of the treatment, the doses of

the treatment, the specific agents that are used, I really have no expertise in that area. I deal more with the general issues and I deal with the oncologists.

Q Do you consider yourself to be an expert in the field of cardiology?

A No, sir. Again, I have some knowledge of the pathology of heart disease, but I myself am not an expert in the diagnosis of heart disease in living patients, and I am not an expert in the treatment of heart diseases.

Q I am going to give a little bit of an extension to that question and ask you: Do you consider yourself to be an expert on the causation of cardiovascular disease?

A I think that is an area that is encompassed by general pathology, causation of heart disease is a topic that is discussed in great depth in general pathology textbooks, that is an area that I feel that I have some background in. Again, I don't treat people with heart disease, I don't make diagnoses

based on examination of radiographic studies or electrophysiologic studies, I really have no expertise in that area, but the causation and pathogenesis of cardiac disease is something that falls more under the general topic of pathology, general pathology.

Q Do you have any expertise in cigarette design or manufacturing?

A No, sir.

Q Any expertise in hospital administration?

A I unfortunately have a number of administrative responsibilities. I would not call myself an expert in hospital administration. I would like to deny all of that area, if I could. I do not consider myself primarily an administrator.

Q Okay.

Do you have any amount of expertise in medical economics?

A No, sir.

Q Do you consider yourself a molecular biologist?

A Yes, sir. I consider myself active in

molecular biology, molecular pathology research.

Q Do you have any knowledge of the Mississippi Medicaid system of reimbursement for health care costs?

A No, sir, not at all.

Q Do you have any expertise with regard to apportioning smoking-attributable health care costs?

A No, sir.

Q Doctor, do you have a customary fee that you charge for consulting in litigation?

A Yes, sir.

Q What is that fee?

A I charge, for review of medical records or documents or consultation time, $250 an hour, and for time under oath, could be deposition time, testimony time or whatever, $400 an hour.

Q Is $400 per hour what you expect to charge for your time in this deposition today?

A Yes, sir.

Q Is that a fee that you set personally or does Johns Hopkins give you some direction as to what

fee to charge?

A I set that personally after discussing this some time ago with some lawyers as far as what appropriate fees were.

Q Doctor, you have mentioned that you participate with oncologists in making the diagnosis of cancer; is that correct?

A Yes, sir.

Q And your participation in the diagnosis of cancer really goes -- it goes beyond lung cancer, it would really relate to cancers of various sites in the body; is that accurate?

A Yes, sir.

Q Let's start with discussing lung cancer in particular. What is your role in attempting to make a diagnosis of lung cancer?

A The pathologist's role in making a diagnosis of lung cancer usually involves the examination of biopsy or cytology material. For example, if a person suspected to have lung cancer undergoes a procedure, a biopsy procedure, I as a

pathologist will look at the biopsy microscopically and make a determination as to whether or not the cancer is present, and, if cancer is present, give a diagnosis with regard to the histologic type of the cancer.

If the treating physicians elect to treat the patient with a resection, by resection of the cancerous portion of lung, I would evaluate that resected specimen for, again, the diagnosis, that it is cancer and the type of cancer. I would evaluate the margins of resection or the adequacy of the surgical procedure.

I would evaluate lymph nodes for metastasis. I would evaluate the surrounding area of lung tissue for intrapulmonary spread of the cancer. I would also evaluate the cancer itself for the histologic pattern, again, to establish the cell type of cancer as well as a histologic grade of the type of cancer.

That's basically how a pathologist would be involved in the diagnosis of lung cancer.

There are other situations where lung cancer patients present as a result of metastatic disease. For example, a lung cancer patient may present with metastasis to the brain and at the time of presentation it is recognized that they have a lung mass, but it is the brain mass that is biopsied because that is what is causing the clinical problems and the surgeon wants to treat the brain mass, and there I would be again consulted to make a histologic diagnosis as far as cell type of the cancer and to give the treating physicians information with regard to the likely site of origin of the cancer.

The way I communicate this information to the physicians is, first of all, in terms of a report, a written report, and very often there is often a discussion either by telephone or more formally where the oncologists come and meet with me on a regular basis on Friday afternoons. Today is an exception.

Q In the course of your work to arrive at the diagnosis of the lung cancer and also to interact with the treating physicians regarding perhaps information

that would relate to what type of treatment modality to use, do you ever attempt to make determinations of the cause of the lung cancer?

A That's not really my job as a hospital pathologist.

Q Understanding that it is not your job as a hospital pathologist, have you participated in discussions attempting to arrive at a determination of the cause of lung cancer in context to your practice?

A Not on a routine basis. In my experience the vast majority of patients with lung cancers have been cigarette smokers, and there's really not a significant amount of discussion with regard to the cause of cancers in these patients because I think that there's a general understanding in the medical community that the vast majority of these cancers are caused by cigarette smoking.

For some patients there is a question as to whether or not asbestos was involved in the development of the lung cancer. I do not on a routine basis as a diagnosing pathologist look for evidence of

asbestos-related diseases or look for asbestos bodies. If there are obvious asbestos-related changes in the lung tissue that is available for pathology examination, I would make note of that, but that's not something that I actively look for in such a specimen. That's not really part of the job of a hospital pathologist. It really won't make a great deal of difference as far as our recommendations to the oncologist, information that we give to the oncologist.

Q In the course of your handling of the individual patient pathology materials, are you made aware of any of the medical history or otherwise particular information regarding those patients when you are reviewing pathology materials?

A Very often, yes, and I would say in most cases we are.

For example, if there's a lung biopsy, routinely the clinicians will provide us with the information that the biopsy is from a patient with a mass in the lung and a history of cigarette smoking.

They will often detail the extent of cigarette smoking. I would say that that's the usual occurrence. They provide us with some clinical information so that we have an understanding of what they are expecting to find, what they are looking for.

Q Now, you have mentioned one aspect of the history of the patient that is related to you is the cigarette smoking. Do you see any other kinds of information regarding the background of that patient that may relate to risk factors for disease?

A Usually the information that is included will be the age, the sex of the patient, the important clinical finding, which would be a lung mass, and the important factor that the patient has been a cigarette smoker. That's what we typically receive in terms of information.

Q Is that information that you have in advance of examining the pathology specimens?

A Yes, sir.

Q Are you provided with any other information that may relate to occupational history, perhaps

environmental exposures, any other known factor associated with the incidence of lung cancer?

A Typically we are not. On occasion we are provided with information regarding occupational exposure. We are provided with that information particularly on pleural biopsies where there is a suspicion that a patient has mesothelioma.

With regard to lung nodules where the clinical suspicion is lung cancer, we are usually not provided with information as to whether or not the patient was occupationally exposed to asbestos. On occasion that's provided, but I would say that that's not the usual, whereas whenever we have a biopsy for a lung mass, we virtually always have information as to whether or not the patient was a smoker.

Q Doctor, now thinking about this in sort of a tunnel vision approach, when you look at pathology specimens for individual patients, can you, for instance, looking at lung cancer specimens, identify what the causal factor may be for that particular lung cancer by the appearance of the tissue or otherwise

some type of a particular marker that relates to, say, an exposure that brought about the disease process?

A Well, there is nothing specific about the pathology of the cancer itself to indicate what the cause of the cancer was. I think we fall back on our general medical knowledge with relation to cigarette smoking causing lung cancer, and based on that, that close association, I can reason that virtually every lung cancer that occurs in an individual that has smoked cigarettes was caused by the cigarettes at least in part.

Q So in your view everyone who has ever smoked, if they at some point in their life after that smoking exposure developed lung cancer, then you would conclude that their lung cancer is caused by cigarette smoking; is that correct?

A Basically I would say so. That's assuming that they have been exposed to at least some significant level of cigarette smoking, cigarette smoke, and I would make the conclusion that their lung cancer was caused at least in part by the cigarette

smoke.

Q What would you consider a significant exposure to cigarette smoke?

A I haven't really sat down and thought about that carefully so I could define that. Unfortunately, I think a very large number of people have had a significant cigarette smoke exposure even if they have not been smokers, because there's good evidence that sidestream secondhand smoking causes a large increase in cancer incidence, lung cancer incidence. That means that a very large percentage of people have had significant exposure to cigarette smoke. Again, I haven't really tried to define what I would call significant.

I think that living in a household of an individual that smokes cigarettes in that same house would probably fall under the category of being a significant exposure. An individual who themselves have smoked cigarettes for at least a year, at least a half a pack per day, probably already reaches a level of where it is a significant exposure. Anything below

that I don't know, I haven't really sat down and tried to define what is significant, what is not significant.

Q Apart from recognizing that there are active smokers in society that of course would be exposed to cigarette smoke, is it your view that anyone who would be a nonsmoker would have a significant exposure of tobacco smoke by virtue of sidestream or environmental tobacco smoke?

A Well, many people have because they have lived in a household of a smoker or they have been exposed to sidestream smoke in the workplace. In fact, that extends on to encompass an enormous number of people. We would have to look hard to find people that have not had any cigarette smoking exposure beyond just very brief and casual exposures. There would probably be very few people in the United States that have never inhaled cigarette smoke.

Q How would you ever make a determination whether they had significant exposure to cigarette smoke if they were never an active smoker?

A I think that can be done only by history: Trying to determine whether or not there was a cigarette smoker in their family that lived in the same household that they lived in, or by determining if they worked in a workplace environment where there was active smoking.

Q Do you have any expertise in statistics?

A I use statistics in my research, yes.

Q Are you familiar with the use of relative risk numbers to describe an association between a factor and a disease process?

A Yes. Relative risks are determinations that epidemiologists make in general, they make relative risk determinations after observations of past trends, and this is an attempt to predict what will happen in the future, or what would happen in the future if certain patterns of behavior are followed.

Q Do you know how to calculate a relative risk, Doctor?

A I think I could if I were provided with data, yes.

Q Can you describe for me how you would calculate a relative risk?

A Sure. One first tries to establish a background level of a disease, and that is actually one of the -- that is one of the most difficult aspects of the entire work of trying to determine a relative risk.

One sets that background level arbitrarily as a relative risk of one. Then the epidemiologist looks at the incidence of a disease in a population with a specific exposure or under a certain condition of life style, compares the ratio of the disease in this particular population to that of the control population which has supposedly not had any of the same exposure, or has not had any of the same type of life style, and expresses that in terms of a ratio to the arbitrarily set risk value of one.

Q Would you agree, Doctor, that if you have relative risk figures calculated for some particular factor that fall below the relative risk of two that there is a significant question regarding whether you

have a true association?

A I don't think a statistician would agree with that. I think the power of your statistical conclusion depends upon the relative difference, which is the issue that you have addressed, the size of the populations sampled, the fundamental scientific logic that underlies the conclusion.

Q Is it your view that you could be accepting of a relative risk figure at any level above one as being a reliable figure for describing a true association between the factor and a disease process?

A Yes, sir. And I can give you an example.

The relative risk of someone dying in an automobile accident, if one compares the relative risk of people that drive while reading a newspaper at their side, that may not exceed two, that may be 1.5, maybe 50 percent greater than the risk of the general population.

I am assuming that whoever did this study has sampled a large group of people and that that's a large group. I would accept that because it is very

logical to me that somebody who read a newspaper at their side is going to be at increased risk of getting into an automobile accident and dying.

If you were to take a small sample of people, and in the small sample of people you would define people under five-feet-eight are at a 1.5 greater risk of getting into automobile accidents than people over 6 feet tall, or whatever, and this was a small sample, I would not accept that because there's no apparent logic there and because you have a small sample. I would say that that's something that really needs further proof.

Again, I think the factors that we look for here are the power on the statistical conclusion which requires that we look at the sample size as well as the logic and the scientific basis underlying the conclusion, not simply the statistics by themselves, but the logic underlying that.

Q Right.

You are also familiar, Doctor, aren't you, with the concept of confounding factors in the context

of epidemiological studies?

A I am aware of the term, yes.

Q Can you tell me what that is?

A Confounding factors I understand to refer to factors other than the main factor which is being tested in the study but which may also contribute to an outcome.

Q In evaluating whether or not you can be accepting of a statistical association as a true association, isn't it important to make a determination of or control for potential confounding factors that may be present in the population studied?

A Yes, sir, it is. Again, I think that would fall under what I described as the logic or the scientific soundness of a conclusion. One must consider what confounding factors could have contributed to an outcome, examine the data to see whether or not those confounding factors could have played a role, try to design the studies so that the confounding factors are considered in the design of the study. I believe that those are all important.

Q Have you evaluated the epidemiological literature regarding environmental tobacco smoke or, as it's generally called, passive smoking?

A Yes, sir, I have. There have been -- I particularly remember reviewing some of the studies on incidence of lung cancer in spouses of smokers.

Q Are you familiar with the relative risk calculations that have been made in the context of those studies?

A Yes, sir.

Q What relative risk levels are you familiar with with respect to environmental tobacco smoke?

A They are on the order of twofold risk for the individuals that have had apparently heavy bystander exposure to cigarette smoking.

Q Are you familiar with the relative risk figure that has been estimated by the Environmental Protection Agency for environmental tobacco smoke?

A I don't know what figure that they have used.

Q Did you make any attempt to evaluate those

studies for their design with regard to the extent to which they controlled for potential confounding factors?

A Yes, sir. When I read those, I am certain that I looked at them for their scientific soundness, and although I cannot recall the specifics of those studies, I do believe that they did account for confounding factors.

Q What confounding factors were controlled for in those studies, Doctor?

A Well, in particular they tried to account for all cigarette smoke that these individuals had been exposed to. They tried to account for other occupational exposures. I believe that some of the studies or maybe the majority of the studies had even tried to make some accommodation for radon exposure.

Q Anything else?

A Not that I recall at this time.

Q You mentioned that in examining the pathology tissue with respect to an individual that there would be no particular appearance or marker to

look for in that tissue that would identify its specific cause in terms of some environmental exposure, or, if it is cigarette smoke, what actually caused the cancer; is that correct?

A Well, in the routine examination, the routine histologic examination of cancerous tissues, we do not attempt to assign a cause to that cancer. When we examine a lung that has been resected for lung cancer, we often find incidentally other disease processes that will be indicative of what was the cause of it.

For example, we may see asbestosis as an incidental finding. We may find severe emphysema as an incidental finding. In both of those situations we would certainly have evidence that could help assign a cause, but that again is not part of our routine work.

As far as examination of the cancerous tissue itself, routine pathologic examination, light microscopy, will not yield any information that will specifically implicate a cause for that cancer.

Of course, with all the other information

that is available in the scientific community, one can make, I think, a reasonable assessment of the cause if that was requested, but again, that routine light microscopic examination does not provide information as to what the cause was.

Q If we look beyond light microscopic examination to more particularly the field of research in molecular biology, is it fair to say that there are no specific markers identifiable in the field of molecular biology with respect to cancers to specifically identify the cause of an individual's cancer?

A I would not agree with you there. Molecular biology is not used on a routine basis now for attempting to attribute causation, but there have been described some fingerprint genetic changes that are characteristic of a cigarette smoke injury.

Q Would you be able to take a specific lung cancer specimen without any other knowledge regarding the individual's exposures, behaviors, whatever the case may be, analyze those tissues on the molecular

level, and be able to determine the specific exposure responsible for the development of the lung cancer?

A In many cases, yes, we could do that to a reasonable degree of medical certainty.

Q What types of markers are you referring to that would allow you to do that?

A Well, specifically there are alterations of the p53 tumor suppressor gene that appear to be specific for tobacco-induced genetic damage.

Q So all lung cancers caused by cigarette smoking would contain the p53 mutation?

A No, sir. That's not true. Only approximately 60 percent of lung cancers caused by cigarette smoking will have mutations of p53, and of those 60 percent only half or so would have this characteristic mutation. But of those cases with the characteristic mutation we could say to a reasonable degree of medical certainty without any history of cigarette smoking that that injury was caused by tobacco smoke.

Q Doctor, let's back up a bit and see if I

can get a better understanding of what you regard as markers for cigarette smoke in lung cancer.

The p53 mutation that you are referring to is a mutation of DNA material within the cell; is that correct?

A Yes, sir.

Q Can you give me a brief description of how DNA plays a role in the function of cellular activity?

I know that is a broad question, but I am talking about sort of starting with the fundamental, and then we can walk our way through it.

A I will try.

DNA is a molecule that forms chromosomes. The DNA is comprised of nucleic acids that are arranged in specific sequences, and sets of these sequences are in code structures that we call genes. Each normal human cell will have 46 chromosomes and each chromosome will have thousands of genes, so each human cell has several hundred thousand genes.

The genes encode for most cases proteins, although some genes appear to encode RNA, which is by

itself active, and these proteins will have a role in the cellular structure or physiology. These proteins either help determine the structure of the cell, keep it together. Other proteins will determine the metabolism of a cell.

With relationship to cancer, some of the proteins have roles in controlling cell division. Some of the proteins have roles in controlling migration of the cell or cellular localization within the body.

Do you want me to go on describing what we know about genetic changes of cancer and how that affects proteins?

Q We will hold it right there for the time being and see if I can take this through in a step-wise basis to sort of break it down.

Each chromosome then is composed of DNA, long strands of DNA; is that correct?

A Yes, sir.

Q And you have got 23 sets of chromosomes within each cell; is that correct?

A We have 22 pairs of chromosomes, and then we have two sex chromosomes, men have one X, one Y chromosome, women have two X chromosomes.

Q Now, when you hear people talk about the, quote unquote, human genome, they are referring to the attempt to map out the structure and the activity of the DNA contained within all of these chromosomes you have just described; is that correct?

A Yes, sir.

Q Now, in the attempt to identify the structure and function of the human genome, what proportion of the human genome currently has been identified and is understood with regard to its function in cellular activity?

A I don't know that I can answer that question. There was an edition of Science just a few weeks ago on the status of the human genome project, and I forgot what percentage of the human genome had been sequenced. It may be approaching something on the order of 30 percent, maybe it is lower than that, but at that level we still don't understand what all

of those sequences do, whether they are introns or exons, what the specific genes are, what the structures of the genes are, many of the more complex issues here, the project is still at a relatively early stage, although it has, I think, made remarkable progress.

That is a systematic approach to try to define the entire human genome. I think it is a very worthwhile project.

What has been done by individual investigators for many years now is to study either particular regions of the genome of interest or to study function and disease and bring those studies back to the genetic level.

One example of where a genomic area of interest has been studied would be the efforts to isolate the BRCA1 and BRCA2 genes that are linked to hereditary breast cancer. It was known that those hereditary predispositions were linked to certain regions of the genome, and microbiologists used positional strategies to find out what was in that

area of the genome, a very intensive effort to identify what was in a particular region of a genome, isolate a gene, test the gene, ultimately determine which genes were involved here.

Moving back from a functional standpoint is the way many genes have been discovered, and in fact that is how the p53 gene was discovered. It was not discovered by the human genome project. The p53 gene was discovered by Dr. Levine at Princeton who found a cellular protein that bound to the SV40 virus. Ultimately that protein turned out to be p53. It took some time before it was discovered where that gene mapped in the human genome.

It was later found that that gene was mutated in human cancers. It was even later that it was found what the consequences of that mutation meant in terms of cell physiology.

Other investigators found what mutations were characteristic of lung cancer in particular and of lung cancers caused by tobacco injury. There's been a steady progression of research, but it did not

originate from the human genome project with regard to p53.

Q Do we now know all of the functionally active regions of the human genome that constitute part of the carcinogenesis process for lung cancer?

A No, sir. We know that there are regions of frequent allelic loss of a number of chromosomal arms in lung cancer, and I think we reasonably expect to find tumor suppressor genes on these chromosomal arms.

There has also been some recent data that we have not yet published to show that there are amplifications of at least two chromosomal arms that commonly occur in lung cancer. We have not yet defined what those genes are.

Q When you refer to allelic loss, you are referring to a mutation; is that correct?

A In the general sense, yes. A mutation I think can be defined as a permanent and heritable alteration of chromosomal material.

Q How many different genes are hypothesized to compose the human genome?

A A very large number, and I apologize if I am not current on what the exact number is. I believe it is on the order of 100,000 genes.

Q So based upon your testimony, we may have identified perhaps 30 percent of the genes in the human genome at this point?

A No. The human genome project has extensively characterized 30 percent of the genome from a sequence level. That does not mean that we have identified the genes there.

I don't know how many thousands of genes have been identified, but we are still on the order of having identified only a small percentage of all of the genes that we believe exist in the human genome.

Q What is your best estimate at this point of how many genes have been identified, in terms of a percentage?

A I am going to estimate 10,000.

Q So that would be roughly, maybe, 10 percent of all the genes composed in the human genome?

A I think that's a crude but reasonable

estimate.

Q Within all of those genes that you have referred to as identified, do we understand all of the active portions of those genes and the inactive portions of those genes with respect to cellular biology?

A No, sir.

Q What proportion of this 10 percent of genes identified do we have an understanding of the active portions of the genes and the inactive portions of the genes?

A Well, that's impossible to say because much of what we don't understand we don't even know that we don't understand. It would be like asking everybody who is absent in this room to raise their hand.

Q So there's a lot more to be explored in this whole area of genetics in order to have a full understanding of cellular biology?

A Yes, sir. I don't anticipate that in my lifetime we will fully understand all of cellular biology. I don't anticipate that in my lifetime we

will find a cure to all types of cancers.

Q Do we have a lot of research to conduct to have a full understanding of the possible contribution of genetics to the cause of a particular cell type of lung cancer?

A If you are speaking of the contribution of genetics, I don't think, again, that there is any doubt in the scientific community that cancers, all cancers are the end result of altered chromosomal material, chromosomal mutations, chromosomal changes that result in cellular changes. We don't understand what all of those chromosomal changes are, but I don't think we need to -- we are not at the level where we are not sure that all cancers are caused by chromosomal changes. I think we have certainly come to that level where we understand that.

Q That same point would apply to lung cancers?

A Yes, sir.

Q Doctor, would you define for me what epigenetic change is?

A I hear the term used very often, and I am not sure that I can define it, and I don't believe that people who use the term really know what they are talking about.

Epigenetic, I believe, is generally referred to as a change, even a transmissible change, that is not specifically related to alterations of chromosomal material.

One reason that I have expressed that I think people don't really understand exactly what epigenetic means is that DNA methylation is a common alteration of DNA that is referred to by some people as epigenetic in that it does not by itself change the sequence of the DNA nucleotides, yet methylation is heritable, it is transmitted from one cell to the other, it results in altered cellular function.

It is not entirely permanent because methylation is potentially reversible, although once methylation changes have occurred and passed on to daughter cells, I cannot think of examples readily where it does reverse, although it is potentially

reversible, and in that sense it is different than a mutation.

So I think methylation is an example of what is commonly referred to as an epigenetic change, but I don't think that people really have a full understanding of the implications of methylation.

Q Do scientists in the field of molecular biology, do you personally know whether it is the genetic changes or the epigenetic changes that are really more important in lung cancer carcinogenesis?

A Well, every change that occurs and contributes to the process is important, and I don't think you can say one is more important than another.

An analogy I would use is a basketball game. You can't say that one basket is worth more than another one. It still counts the same two points as the first basket.

An epigenetic change may not appear to be as dramatic as a mutation of a well-known tumor suppressor gene, but from a functional standpoint it may be very important for the development of the

cancer.

Q Do we know the factors, that is, perhaps environmental factors, other considerations that would account for or cause these epigenetic changes that are considered in the context of carcinogenesis?

A There's some recent data. Actually this is some of the work that I have been referring to that is not yet published. NNK, which is a tobacco specific carcinogen, has been found to induce methylation of the promoter region of the tumor suppressor gene MTS1, also known as p16, in lung epithelium.

I am not aware of other studies of tobacco specific carcinogens and methylation.

I should go back a little bit. Some people refer to the process of tumor promotion as an epigenetic process. I prefer not to because I think that that confuses the issue as far as what the process of tumor promotion is. But as far as tumor promotion is concerned, people have conducted experiments with regard to tobacco smoke condensate and found that tobacco smoke condensate has similar

tumor promoting properties to a well-known experimental tumor promoter TPA.

Q TPA, otherwise regarded by the term four ball ester?

A Yes, sir. A four ball ester is the general class of chemicals, and TPA is probably the most active of that class of tumor promotion.

Q Let's back up a bit to your participation in some of the research that you get involved with within this field of molecular biology.

How would you describe the nature of your research that you have conducted during the time that you have been involved in cellular genetic research?

A Well, it occurs on several levels. I am a pathologist, and much of my involvement is as a pathologist. I also have a laboratory with two postdoctoral fellows, two technicians. These people do benchtop molecular biology work that I direct.

With regard to many of the lung cancer studies, I work with molecular biologists who do parallel work, and these molecular biologists don't do

the work of a pathologist, so much of my participation has been to provide the pathology expertise from the perspective of somebody who understands exactly what they are going to be doing at the benchtop.

Q What exactly is it that you contribute within this team of people researching these topics that you publish on?

A Well, I can give you an example. I have done a considerable amount of work with Dr. David Sidransky where we have looked for chromosomal losses in lung cancer, alterations of microsatellites in lung cancer. Much of this work has been -- much of my work here has been to, first of all, provide the lung cancer tissues, to conduct microdissections of these tissues so that the person doing the benchtop work has an optimal sample, to review the data with a person who is doing benchtop work, so if they come up with an unexpected result, to determine whether or not it's an exciting finding or whether there could be some trivial explanation and whether or not we should go back and reanalyze it in a different manner. That has

been to a large extent the way I have participated in most of these lung cancer research projects.

As I said, my laboratory does the molecular studies, is capable of doing these molecular studies, but we simply don't have the number of people to do all of the work ourselves. I have these collaborators that are very anxious to do these molecular studies but really need this support from a pathologist, so much of my practice has been more from the standpoint of being a pathologist with an understanding of what they are doing in the laboratory rather than the person who actually does the benchtop molecular biology work or directs the benchtop molecular biology work.

Q Okay. You don't direct the benchtop molecular biology work?

A Well, I do. Actually I have done more direction of benchtop molecular biology work for my breast cancer studies than I have for the lung cancer studies, and the lung cancer studies are being done in Dr. Sidransky's lab, Dr. Steve Baylin's lab. I work

closely with these people, probably as closely as I do with the people in my own lab, but as I said, these people are very anxious to do these projects. They are looking for my support. I consider myself a collaborator. I think it would be inappropriate for me to say no, I can do the whole project myself, I will do it myself. In fact, the people in my lab are overwhelmed with the amount of work in front of them. I am happy that somebody else is anxious to do this work.

Q So that with respect to your research on lung cancer, is it fair to say that Dr. Sidransky's lab does the benchtop molecular biology work on those studies?

A The fellows in his laboratory in general have done the benchtop work in terms of doing molecular biology reactions, running jells and so on. There have been some of the studies that have been done in Dr. Baylin's laboratory by fellows from his laboratory of a similar nature.

Q For instance, if a particular study

required the polymerase chain reaction procedure to identify genetic changes, that would be done in Dr. Sidransky's lab?

A It may be. We do that work in our lab. As a part of our -- some of our ongoing studies, we want to see if there's loss of chromosome 9 in in situ squamous carcinoma. Questions came up who is going to do that. I could do it. Somebody else has more time, I am happy to let them do that work. I am happy to provide the materials to do the work that only I am capable of in this team and pass the other work on to somebody else.

Q Do you in the course of the lung cancer research provide the cell culture materials for some of that work?

A We actually have not used a great deal of cell culture material in our recent work, and I have not provided any of the cell culture material for several years. I have in the past, but I have not recently. Again, those are now considered to be relatively routine, and there's technical staff

available for these fellows to provide that support.

Q In the research that you are doing regarding these genetic changes observable in lung cancer, where do the tissues come from?

A These are from patients that were seen at Johns Hopkins Hospital or Johns Hopkins/Bayview Medical Center.

Q So that with respect to the tissues that you are describing that are involved in this research, are we looking at some type of molecular epidemiological approach to the study of this area, or what is the most appropriate description of the procedure that you are using to do the research?

A We are really not undertaking these studies with the intent of using them for molecular epidemiologic studies, or we are not attempting to define a Maryland population, we are not attempting to define any one particular group of individuals. We are trying to learn more about the molecular changes that are important for lung cancer development.

I think if, for example, we find an

important molecular change, for example, we have described frequent inactivation of the MTS tumor suppressor gene by methylation, it would be a worthwhile study for someone to do a molecular epidemiologic study looking at different populations across the country. We have no immediate plans to do that.

Q The MTS tumor suppressor gene that you are referring to is the gene on chromosome 9?

A Yes, sir.

Q That is where you focus most of your research effort, is that fair, with respect to lung cancer?

A That has been a focus of considerable research effort. I really wouldn't say that that's my major focus of effort. In fact, we are trying to find other genes that are involved in lung cancer development.

Q So the p16 gene that you refer to, chromosome 9, is really only one of the tumor suppressor genes that your lab has actively explored

as a possible contributor to the carcinogenesis process?

A Yes, sir. That is only one of the genes that we are exploring or planning to explore in our efforts to understand what lung cancer is about.

Q How many other genes is your laboratory working on, or has it worked on, in an attempt to identify or explore the function of the gene in lung cancer carcinogenesis?

A I have a fellow in my laboratory who is trying to find a tumor suppressor gene on chromosome 6. This chromosomal region is commonly affected in lung cancer, breast cancer, melanoma, mesothelioma, probably other types of cancers. Most of his work uses breast cancer samples, although he has also looked at lung cancer samples, but his work now is really trying to define very precisely the chromosomal region affected and then find the gene there.

At this stage his work is at a very fundamental level. We know that gene is important because of our broader studies looking at the human

cancers. Now we are moving into a very fundamental level trying to find the gene.

If and when we find this gene, we would move back to a level where we would look at its involvement in lung cancer, its involvement in breast cancer, its involvement in other cancers. That's an area where my laboratory is putting a great deal of effort now.

In my collaboration with Dr. Joseph Testas, at Foxchase, we have found frequent amplifications or apparent amplifications on chromosomes 3 and chromosome 5 and lung cancer. We are hoping to finish up that work from a preliminary standpoint and publish that relatively soon. Dr. Testas has been using that technique known as competitive genomic hybridization to define this amplification. Then we have to make some decisions about how much effort will be devoted to trying to find the genes that are amplified and who will do it, who will take the lead in doing that.

Q In your view, it sounds as if this is an exceedingly complex area to explore, that being the

possible genetic events involved in carcinogenesis; is that correct?

A Well, there are many genes involved and it is a complex situation. Cancer is a complex disease.

Q Can it be described as a single disease, that being lung cancer?

A I hate to either agree or disagree with the definitions that are provided to me. In general, cancers of all organs are more like each other than they are different. They share many common traits.

With regard to lung cancer, cancers of the lung are more alike than they are different. For example, we know that cancers of the lung of all histologic types have frequent mutations of the p53 gene. It's most common in small-cell cancer of the lung, squamous cell cancer of the lung, less common in adenocarcinoma of the lung, but they are similar in that they share this genetic alteration.

Alterations of the MTS1 p16 gene are also seen in all types of lung cancers, less so in small-cell lung cancers and non-small-cell

lung cancers. Chromosomal loss of 6q is commonly seen in all types of histologic patterns of lung cancer.

We believe that all of these lung cancers share a number of features on a molecular level, anatomically they share a number of features and often histologic types are mixed, both tumors will have both small-cell and non-small-cell histologic patterns.

I don't think that we should consider cancer a number of different diseases. It's really one disease with a set of molecular alterations that are not the same in all cancers but many components of which are shared among the different cancers.

Biologically there are differences in behaviors among the different cancers, probably related to these differences in molecular changes, but still basically it is a one-disease process.

MR. KEMNA: Let's take that break for lunch now.

(Luncheon recess -- 12:30 p.m.)

Afternoon Session (1:30 p.m.)

(Defendants' Deposition Exhibits Nos. 4

through 10 were marked for identification.)

BY MR. KEMNA:

Q Doctor, is all lung cancer caused by cigarette smoking?

A No, I think it is safe to say that there are lung cancers that are most likely not caused by cigarette smoking.

Q What fraction of all lung cancers would you attribute to being caused by cigarette smoking?

A Well, I kind of recall the Attorney General saying about 85 percent of lung cancers as being caused by cigarette smoking, and I think that's probably a reasonable estimate. Perhaps even a higher percentage of lung cancers have had some causation by cigarette smoke in terms of bystander exposure which is difficult to assess, but it is reasonable to say that at least 85 percent of lung cancers in the United States have been caused by cigarette smoking, at least in part.

Q I think you mentioned in the context of that answer the Attorney General. I assume you meant

the Surgeon General?

A I'm sorry, the Surgeon General. I haven't quite gotten my mind back into gear after lunch.

Q So your opinion about the attributable fraction of lung cancer that is caused by cigarette smoking is really your reliance on the Surgeon General of the United States. Is that --

A I am relying on those figures for coming up with a number. From my own observations, almost all lung cancers that I have seen as a pathologist or since I began professional training for medicine have been associated with cigarette smoking. I haven't attempted to document that. I haven't attempted to do any controlled studies. So if you ask me to come up with a percentage, I am relying upon published data which has been summarized by the Surgeon General, and just based on my own experience I would say that that's a reasonable assessment.

Q Which report of the Surgeon General are you referring to that this figure came from?

A I forgot. It was in the 1980s sometime. I

forgot exactly what the date of that was.

Q You would agree, wouldn't you, Doctor, that a statistical association between a factor and a disease process is not the same as saying that you have established a cause and effect relationship between the factor and the disease process?

A Are you referring to, like, an epidemiological statistical association?

Q Yes.

A An epidemiological statistical association is not by itself sufficient to say that that association is equivalent to causing.

Q What else do you need to know before you can make a determination of the cause and effect relationship?

A Well, my mind is working in the frame of cigarette smoking and causation of lung cancer. I would first of all need to know that the agent that is suspected of causing the cancer reaches the target cells where the cancer originates. That's obviously true for lung cancer. People inhale cigarette smoke.

It is applied directly to the target cells.

It is useful to know if there have been any experimental models to provide support of evidence, supportive evidence for the concept of causation. In terms of lung cancer there are a large number of experimental models in terms of animal studies, in terms of in vitro studies.

It is useful to have mechanistic data available, and there is in terms of lung cancer and cancer causation on a number of levels, there has been data available for many years to demonstrate that cigarette smoke contains mutagenic agents. That's been known for a long period of time.

Coming up to the present time, there is evidence that the specific mutagenic agent in cigarette smoke, benzpyrene, causes the specific genetic alterations that are commonly observed in lung cancers.

I think the aggregate of this in terms of cigarette smoking and lung cancer is overwhelming. In fact, I think one could remove different pieces of

that and still have a story that would allow one to conclude to a reasonable certainty that cigarette smoking causes lung cancer.

Q Let me interrupt you for just a moment.

I know that your mindset is on cigarette smoking, but my question is really directed to a more generic level.

What I am saying is, and we started with a discussion of looking for information that would be supportive of an association between a factor and a disease process, and recognizing that just simply that information alone is not sufficient to make a causal conclusion, what are your criteria for determining a cause and effect relationship between a factor and a disease? And let's not relate it specifically to cigarette smoking, but I would like to know what the thought process is that brings you down to the conclusion of cause and effect.

A My thought process looks for mechanisms, for some explanation as to why an agent could cause cancer in addition to having this epidemiologic

association, statistical association, I would want to see some explanation as to why that agent would cause the cancer, data to show this mechanism.

Q And what is the nature of data that you would have to rely on to show the mechanism that you are describing?

A I think that that's variable. It depends on the individual situation.

If one were to want to draw an association between driving a particular brand of an automobile and getting lung cancer, to me there would be no obvious explanation for that. If one were to find a statistically significant association, I would question as to whether or not there may be some finding there, but until someone were able to demonstrate a likely mechanism for this association, I would not be able to accept driving a particular brand of automobile as being causally related to developing lung cancer.

On the other hand, if you are talking about driving a particular automobile and the risk of dying

in a head-on auto accident, I think even without a great deal of data to show what the structural characteristics of that car are, it seems logical to me that if there are a large number of auto accidents that have been analyzed, head-on collisions, and one particular automobile stands out in that the drivers of that automobile always get killed in head-on collisions, I would not need a great deal of mechanistic data to conclude that more likely than not that that is a dangerous automobile.

Q Let's talk about an example that relates maybe a little bit closer to what we are talking about.

Let's say for the sake of discussion you have a statistically significant association established between cigarette smoking and cirrhosis of the liver. How would you go about making a determination of whether or not there was a cause and effect relationship between cigarette smoking and cirrhosis of the liver?

A That's a good example, and it would not

immediately be apparent what in cigarette smoke would cause damage to the liver.

I would look for some evidence that there is a component of cigarette smoke that the liver is exposed to in some manner, first of all. It is apparent that the lungs are exposed to cigarette smoke. It is not immediately apparent, without additional data, that the liver is exposed to cigarette smoke component. I would want that type of evidence, that the liver is exposed to some cigarette smoke component.

I would also want evidence that such a component of cigarette smoke that the liver is exposed to causes some damage to the liver.

Actually, going back to your original hypothetical, I would probably look carefully at the epidemiologic data to see if there is -- what you brought out before -- a confounding factor. Do cigarette smokers consume more alcohol. We all recognize that alcohol causes cirrhosis of the liver. Excess alcohol consumption.

So I think I would begin by evaluating epidemiologic studies, and then I would look at the likely mechanisms by which this agent could cause the damage that you are attempting to associate with that agent, and if I see that one can establish these other links and if that epidemiologic evidence were very strong, I would at some point conclude that cigarette smoking caused cirrhosis of the liver.

Q Is it your opinion that cigarette smoking is involved in the cause and effect relationship with cirrhosis of the liver?

A No. That is not my opinion.

Q So the key in the example that we are talking about regarding the association between cigarette smoking and cirrhosis of the liver, the key that allows you to differentiate between a consideration of smoking and alcohol, for instance, is an established mechanism for the disease process?

A I don't think the entire mechanism needs to be established. I think some critical issues need to be addressed.

For example, if we did find some component of cigarette smoke that was volatile and entered the bloodstream, was transported to the liver, and we found that that was a very toxic compound that caused liver damage as assessed by a number of animal studies and perhaps also cell culture studies showing it caused damage to human hepatocytes in culture, and if we looked at the epidemiologic studies and they were carefully conducted and they excluded confounding factors such as excess alcohol consumption, I would not need to know every detail of the molecular mechanism.

I think there need to be key points of the mechanism that are identified and are clarified before one can reach a conclusion, but I don't think that one needs to know every minute detail of the mechanism. I mean, ultimately we will never know the minute detail of any mechanism. We can bring things to a molecular level, then we would be challenged to bring them to an atomic level or a subatomic level. It can go beyond reason. We can conclude to reasonable certainty that

alcohol, excess alcohol consumption causes cirrhosis of the liver. That was concluded well before many of the details of alcohol metabolism were well-understood.

Q With respect to lung cancer, Doctor, is it fair to say that the epidemiological studies that have been reported, published on this topic have utilized mortality data to describe the relationship between factors and the disease process of lung cancer?

A I will have to confess that you have asked me a question that I realize I don't know the answer to. I am not sure how many of the studies have looked at lung cancer mortality or simply lung cancer incidence. I know that at least some have looked at lung cancer incidence rather than lung cancer mortality, but I cannot tell you study by study which have looked at incidence as compared to mortality.

Q Can you tell me your familiarity with specific epidemiological studies between cigarette smoking and lung cancer?

A Well, there is a large study conducted by

the American Cancer Society. There is a large study of British physicians. There was a large Veterans Administration study. There have been studies in numerous other countries, in Japan, a large number of other studies. These are the larger studies that are commonly referred to in the medical literature.

Q Have you actually read those studies?

A Some time ago, yes.

Q Do you know whether any of those are ongoing studies?

A Not that I am aware of.

The most recent epidemiologic study that I recall reading was one published by some investigators from University of Michigan School of Public Health, and they looked at lung cancer incidence by age among smokers and former smokers. I don't know if that's an ongoing study from University of Michigan or not.

Certainly the studies that were conducted of British physicians, I believe that they have done follow-up studies on cessation of smoking, I don't know if they are ongoing or not.

Q In the study supported by the American Cancer Society, do you know whether that study was based upon mortality data?

A My recollection is that they examined death certificates, but I may be wrong on that. That may have been a mortality data study.

Q Okay.

What kind of information is included on death certificates?

A It varies. It varies from state to state because each state has a different form for a death certificate, and it varies by physician, whoever fills it out. Unfortunately, I believe that few physicians have been specifically instructed on how to fill out a death certificate, and so that's often problematic in that information on death certificates can be misleading, it can be erroneous, it can be incomplete.

That should not be a problem with regard to the issue of lung cancer, however, with few exceptions, because, first of all, lung cancer is the usual cause of death among people who have lung

cancer, and so it will usually be listed on the death certificate.

Unfortunately, some doctors will put as a cause of death cardiorespiratory arrest due to lung cancer, and in my opinion that is not the way a death certificate should be filled out, but I have commonly seen that done.

Another problem is that sometimes physicians will put lung cancer as a cause of death when in fact the patient had a mesothelioma, it is a cancer affecting the lung, but a physician who saw the patient in a terminal state just listed lung cancer generically as the cause of death.

Usually, however, that does not prevent the epidemiologists who search through death certificates from culling out the cases of lung cancer. It is usually mentioned in some form on the death certificate.

Q What other diagnostic categories might present particular problems with respect to death certificate data and how that may be used in studies

of the incidence and mortality of diseases?

A I don't know. I don't know that anybody has ever undertaken a systematic study of death certificates and how they are filled out and how complete or how accurate they are. I am basing what I say just on my observations.

Q You haven't reviewed any literature or any research that has tried to make a comparison between death certificate data and actual confirmation of diagnoses through autopsy?

A Not systematically.

I recall Dr. Selikoff's study of insulation workers, he tried to determine the incidence of a number of diseases including lung cancer and mesothelioma, and his cohort of individuals, and they made that assessment both by death certificate and by what they called best evidence, where in fact they did some chart reviews and tried to get additional information that was not available on the death certificate. The numbers of cancers were under-represented in the death certificates, but my

recollection is that it was not a huge amount.

That was one study that I think I can point to that documents that there have been problems in documentation by death certificates, but again I am not aware of any study that specifically has looked at how death certificates are filled out and how accurate and complete they are.

Q So beyond your personal experience in your own pathology department, you would not be in a position to opine on the degree to which there may be diagnostic problems on death certificates as compared to autopsy data that would be generated regarding the same subjects involved with the death certificates?

A Actually I should say that when you are dealing with comparing death certificates to autopsy data, you are bringing in a whole new angle. Most deaths are not followed up by autopsy. The overall percentage in the United States is probably 5 percent, more or less. In our institution it is 15 percent, and we just had an inspector congratulate us on the success of having 15 percent of the cases autopsied.

Q Let me just interrupt you for a moment.

Why is it worthy of special recognition to have a high percentage of autopsies at your institution?

A Because we are a training institution, and this is considered to be part of the training of our clinical house staff to get feedback as far as their recognition of all diseases of the patient.

Q I take it that the performance of an autopsy has benefits to it that really relate to better defining exactly what was involved with the patient's disease process and cause of death?

A Well, the autopsy hopefully has educational benefits, and that's the main reason for us to encourage autopsies from the perspective of being a teaching institution.

In fact, when families are approached for autopsies and asked to consent for autopsies, the main reason given to the family for conducting the autopsy is for educational purposes of the physicians. Because it is quite clear that the autopsy will not

benefit the deceased, it is not likely that that autopsy will benefit in any way the survivors by identifying heritable disease. It may answer some unanswered questions, questions that were not answered during life, but most of all it is considered to be a procedure that helps educate the training physicians.

Q Part of the education process of training physicians is to give them feedback on the accuracy of their diagnostic impressions. Wouldn't that be accurate?

A Yes, sir.

Q And the autopsy procedure provides for a more comprehensive review of systems so that that more precise information can be fed back to the medical practitioners; is that correct?

A It may be more comprehensive.

I think a good analogy would be if someone were training to be a singer, it would be useful for that person to listen to a tape recording of their own voice. They would have the opportunity to reflect on what they are doing to have a better understanding of

how this is presented in a more general sense. The training house officer would come down and see organs after an autopsy, would hopefully be able to visualize some of the disease processes that he or she was treating in the patient, and I think it just helps the overall education of the training doctor.

Sometimes autopsies provide a more comprehensive diagnosis. There are other times when autopsies do not add substantially to the diagnosis of a particular case. Even in those situations the autopsy, I think, is still useful for the education of the training physician.

Q Are there times when during life an individual presents with some type of cancer where the primary is unknown, the primary site is unknown and could subsequently be discovered at autopsy?

A Yes, sir, that is a possibility.

Q Do you do autopsies, Doctor?

A I supervise autopsies that are done by pathology house staff at Johns Hopkins.

Q In the course of the performance of

autopsies that you have either done personally or supervised, have you discovered primary sites for cancers that weren't otherwise known during the life of the patient?

A Yes, sir.

Q Did you discover primary sites for cancer that were in locations other than the lung but that the cancer presented itself in the lung during the life of the patient?

A Yes, sir. I think that that's, of course, often recognized by clinicians, sometimes it is not recognized by clinicians, but it is only recognized at autopsy, usually that is recognized --

Q In your personal experience you have observed that happen?

A I have seen some cases, yes.

Q It is true, isn't it, Doctor, that the lung is the most common site for metastases of cancers at various nonlung locations in the body?

A Yes, sir, that is probably correct.

I should qualify that. Lymph nodes are the

most common site of metastases, and lung is the second most common site of metastases.

Q Doctor, would it surprise you if there were studies that reported as high an error rate as 50 percent in the comparison between death certificates and autopsy data regarding the same death certificate subjects?

A It wouldn't surprise me. I guess I would want to know what exactly they are looking for on the death certificate and what they are looking for in the subsequent follow-up study.

It would surprise me if 50 percent of lung cancers were not even mentioned on the death certificate. It would not surprise me if lung cancer were not listed as the number one cause of death in these patients but often cardiorespiratory failure is listed as number 1 and lung cancer as number 2. I think that is very common.

Q Within the scope of what would be regarded as possible diagnostic error between death certificates and autopsy data, would you include the

category of cardiovascular disease diagnosis?

A Again, with death certificates, I believe that there are a number of errors because, as I have said, cardiovascular, cardiorespiratory failure is often listed as a cause of death, number one on the death certificates, even for people that have no significant heart disease. I don't know what the error rate is, but I am aware that there is a significant rate of error in that respect.

Q You would agree, wouldn't you, Doctor, that if your epidemiological study is going to rely upon death certificate data for generating associations between factors and disease processes that it is essential for the ability to rely upon that study for establishing accurate information that the death certificate data be accurate?

A I think that one has to have a certain degree of accuracy in order to be able to rely on the death certificates. If, for example, people filling out the death certificates do not even list lung cancer when individuals are dying of lung cancer,

there is a danger. I think there's a very low risk of false-negatives there in that I do not expect that lung cancer would be very frequently listed for people that do not have lung cancer. I shouldn't say -- I shouldn't call that a false-positive. I do not think that it would be very common for lung cancer to be listed as a cause of death for anybody that does not have lung cancer. I think the error would be in that people who had lung cancer, it was not appropriately listed as a cause of death.

Q Doctor, are you familiar with the term diagnostic bias?

A It's not a term that I commonly use.

Q Do you know what the term means?

A Again, it is not a term that I commonly use, so if I were to see it in context I could probably define it. I would rather not try to define it without knowing what context you are thinking.

Q Doctor, in order to be able to utilize information in death certificates toward establishing some type of statistical association in an

epidemiological study, the death certificate has to display a diagnosis of the disease process in each individual; is that correct?

A The death certificate has to list, either list or exclude the disease that one is surveying for it to be useful for a particular survey.

Q So it would have to include the appropriate diagnosis or cause of death; is that correct?

A I am not sure I understand.

Death certificates in most states have sections for the physician to fill in with regard to cause of death and usually also other significant diseases.

For a death certificate study to be useful, the disease that one is studying should be one that doctors would note if it is present and would not note if it is not present. It would not be useful for someone to use death certificates to study incidence of psoriasis because it is unlikely that doctors would enter a diagnosis of psoriasis as another significant disease. One would have absolutely no idea of what

the incidence of psoriasis is.

Lung cancer is different because lung cancer is a significant disease in everyone that has lung cancer. There will be cases where individuals have lung cancer and it was not the cause of death, perhaps it was successfully treated and was therefore not entered in on the death certificate. There are cases where people would have lung cancer but they die of a different cause, for example, a stroke or a heart attack, and the physician filling out the death certificate would not have included lung cancer in there. There will even be cases where a person dies as a result of complications of lung cancer, but a physician still would enter in as cause of death cardiorespiratory failure due to pneumonia and stop there and doesn't explain that the pneumonia was really a consequence of the cancer. All of those situations will exist, but usually that lung cancer will appear on a death certificate if a patient had lung cancer.

Similarly, if a patient does not have lung

cancer, this is not the type of disease that someone will put on a death certificate. There will be some situations where a person has a cancer of another organ and the physician will put it on the death certificate as lung cancer because it metastasized to the lung. I think that is uncommon. I have seen cases where mesotheliomas are incorrectly classified as lung cancers on death certificates, but other types of cancers are usually called appropriately on death certificates.

So I think for purposes of death certificates, I recognize that there are some errors involved, but I think that death certificates are a relatively reasonable way to assess the prevalence of lung cancer in the population.

Q In order for a diagnosis of lung cancer to be indicated on a death certificate, you would have to have made a determination that in fact the patient had lung cancer, correct, Doctor?

A Yes, sir.

Q What cell types of cancer can occur within

the lungs?

A Well, the four major cell types of lung cancer are small-cell carcinoma, large-cell carcinoma, squamous cell carcinoma and adenocarcinoma.

Q What other cell types of cancer can occur in the lung?

A Well, there are much less commonly sarcomas that are primary to the lung, there are lymphomas that are primary to the lung, there are unusual endocrine tumors that can be primary to the lung.

Q Are lymphomas thought to be caused by cigarette smoking?

A No, sir, I do not consider lymphomas to be linked to cigarette smoke.

Q Are sarcomas caused by cigarette smoking?

A I do not consider sarcomas to be caused by cigarette smoking.

Q Are well-differentiated neuroendocrine carcinomas caused by cigarette smoking?

A Atypical carcinoids, which is the type of neuroendocrine tumor that can result in patient death,

have been linked to cigarette smoking.

Q What is your basis for that opinion?

A There have been retrospective studies, these are case controlled studies, because atypical carcinoids are uncommon tumors and it is not possible to do a large prospective or even large retrospective epidemiologic study. Case control studies have found that individuals with atypical carcinoids more commonly have been smokers than individuals with dissimilar diseases or even other types of lung diseases that are unrelated to neoplasia.

Q Can you cite to me to the best of your recollection what studies revealed this data that lead you to a conclusion that atypical carcinoids are associated with cigarette smoking?

A I cannot recall the specific study at this time. I would be happy to go back and pull that out for you, though.

Q I would like to see that.

Do you remember when this information was published?

A I don't even remember when it was published, but I am sure I can find that.

Q Can you roughly estimate how long ago you became aware of this information?

A I have become aware of that probably in the past five years or so. I haven't seen that many cases of atypical carcinoids, so I really have not paid a great deal of attention to that type of tumor.

Q Is mucoepidermoid a cell type that can occur in the lung?

A There can be mucoepidermoid carcinomas of the lung that are similar to the salivary gland mucoepidermoid tumors. There can also be adenoid cystic carcinomas that are analogous to salivary gland tumors. Those types of cancers have not to my knowledge been linked to cigarette smoking.

I should qualify that by saying that the term mucoepidermoid has been used by pathologists to designate the adenosquamous carcinoma, a conventional adenosquamous carcinoma, which is combined glandular and squamous differentiation. Those conventional

bronchogenic carcinomas are of course linked to cigarette smoking.

When I use the term mucoepidermoid, and I am assuming that you are also using it in this sense, I was referring to tumors that are parallel to the salivary gland tumors. They are very very uncommon tumors.

Q Do death certificates contain any information about the cell type of a lung cancer if they indicate a lung cancer diagnosis?

A Typically not. Probably 95 percent or more of all lung cancers fall under the four major cell types: Small cell, large cell, adenocarcinoma, squamous cell carcinoma. Five percent or less would fall under all of the other categories.

If a patient had a lymphoma, usually that would be designated on the death certificate as a lymphoma rather than as a lung cancer.

If a patient had a primary sarcoma of the lung, it is possible that that would be called a lung cancer rather than a sarcoma of the lung.

But usually when one refers to lung cancer, when any physician refers to lung cancer, it is referring to that larger group that comprises 95 percent or more of all cancers of the lung.

Q Doctor, you used the term bronchogenic.

A Yes, sir.

Q What is the definition of the term bronchogenic?

A Originating from the bronchus.

Q Is that relating somehow to the location in the lung where the cancer originates?

A Not really. The bronchi extend throughout the lungs at least to within a centimeter of the pleura. There are larger bronchi which tend to be more centrally located and smaller branches of the bronchi which tend to be distributed throughout the lungs. Cancers can arise from any of these branches, and bronchogenic cancers arise throughout the lungs.

Q Do you consider the acinus a part of the bronchi?

A No, sir, I don't.

Q What are the different regions of the bronchi that you would consider within the region of what is regarded as bronchogenic carcinoma?

A I consider bronchi related to bronchogenic carcinoma beginning from the trachea and extending all the way down to bronchioles, which are divisions of the bronchi that have no muscular or cartilaginous supporting structures. There is a subtype of adenocarcinoma known as bronchioloalveolar carcinoma. This is an uncommon type of cancer. I kind of recall that it is about one half of one percent of all lung cancers. This cell type of lung cancer has cells that resemble the lining cells of bronchioles. Tall columnar cells make abundant mucin. There is no absolute distinction between this cell type and the cell types that are present in the somewhat larger bronchi. In fact, cancers that arise from these larger bronchi are often adenocarcinomas, and adenocarcinomas very commonly have a portion of the cancer that has an appearance virtually identical to bronchioloalveolar carcinoma. Adenocarcinomas very

commonly have what we call bronchioloalveolar differentiation in a partner tumor.

I think what I am trying to say is that for these adenocarcinomas and bronchioloalveolar carcinomas, that they are very closely related. In fact, bronchioloalveolar carcinoma is considered to be a subtype of adenocarcinoma, so right down to the bronchioles should be considered a part of the bronchial tree.

Q And that's what's composed of your description of the bronchogenic region?

A Yes, sir.

Q Is bronchioloalveolar carcinoma caused by cigarette smoking?

A Yes, sir, it very commonly is.

Q You say very commonly. How do you determine those that are caused versus those that are not caused by cigarette smoking?

A Well, again, there has been found to be an increased incidence of bronchioloalveolar carcinoma among cigarette smokers. Maybe I should qualify that

because the studies that I am aware of were again case controlled studies. I should say that among individuals with bronchioloalveolar carcinoma, a greater incidence of cigarette smoking was found than in the general population, and I would say that probably a majority of bronchioloalveolar carcinomas have been associated with cigarette smoking. There have been a number of these types of cancers that have been described in individuals that have not had a history of smoking, so not all of them are ascribed to cigarette smoking.

This is, again, a small subcategory of all lung cancers, about one half of one percent, and that particular histologic type is considered to not have as strong a link to cigarette smoking as are the other types of lung cancer, other types of bronchogenic lung cancer.

Q Would you agree that some investigators have reported in the literature that there is reason to question whether cigarette smoking accounts for the incidence of bronchioloalveolar carcinoma of the lung?

A I am not aware of anybody who's written anything like that in the past ten years.

Q So as far as you are concerned, there really is no controversy relating to the question of whether bronchioloalveolar carcinoma of the lung is caused by cigarette smoking?

A That's correct. I am not aware of any such controversy.

Q Are you aware of any changes in the relative prominence of one cell type versus another in terms of incidence over the last 30, 35 years?

A Yes, sir.

Q What have you observed about the change in histological cell types?

A Twenty years ago the most common cell type for lung cancer was squamous cell carcinoma. Most recently, I would be referring to data from the early 1990s, adenocarcinoma has been found to be slightly more common than squamous cell carcinoma and is now the most common type of lung cancer.

MR. PATRICK: Can we take a one-minute

break? Go to the rest room.

(A short break was taken.)

(Defendants' Deposition Exhibits Nos. 11 through 13 were marked for identification.)

BY MR. KEMNA:

Q Doctor, let me show you what's been marked as Defendants' Deposition Exhibit No. 13. Just by looking at the title of that article, have you read this article before?

A No, I haven't.

Q Are you familiar with either one of the authors of this article?

A I know a Mark Green who is a clinical oncologist, he used to be at the National Cancer Institute. I don't know if this is the same Mark Green.

Q Why don't you just scan through it for a moment.

A (Witness complying.)

Q Let me ask you to look at page 2379 of Exhibit No. 13. There is a paragraph down in the

middle of the page that begins with: The impact. Right here. Would you read that paragraph to yourself, and I have a couple of questions for you there.

A Okay.

Q The first sentence of that paragraph reads: The impact of cigarette smoking on induction of BAC, which I think we can agree is bronchioloalveolar carcinoma of the lung, is somewhat controversial.

Do you agree or disagree with that statement?

A I don't know if I should agree or disagree with it. I think I would agree that not all bronchioloalveolar carcinomas are caused by cigarette smoking. Maybe I can agree that the extent of bronchioloalveolar carcinomas caused by cigarette smoking is not completely established. If you want to translate to somewhat controversial, I don't think that people are in an active state of argument here. I don't think there is an active controversial argument in the state of the scientific community.

Q So that statement would indicate that you really disagree with whether this is somewhat controversial?

A I think the word controversial is probably not the best choice of words there. It implies that there is some active discord in the scientific community, and I don't really see an active discord. I think that there is different data that leads to different conclusions coming in. People are discussing it, trying to evaluate it, but I don't see a great deal of controversy there.

Q By virtue of the fact there are different data and different conclusions leading up to the publication of this article, which by the way was published in August of 1996, that is not an indication to you that the topic is at least somewhat controversial?

A Well, again, I think that the term controversial is too strong in implying that there are people actively arguing. I don't see the scientific community up there arguing about this. There are

areas in science where people don't talk to each other because their opinions are so strongly different that they will argue with one another. This is not such an area.

Q Well, without the necessity for active argument on a personal level between scientific investigators, you can have a controversy over a particular point in science or medicine without it generating great emotion, can't you, Doctor?

A I guess. To me the term controversial implies more emotion than I think is really present.

Q Look at the first sentence in the next paragraph. The male-to-female ratio of unity also argues against cigarette smoking as a risk factor for the development of bronchioloalveolar carcinoma of the lung.

Do you agree or disagree with that statement?

A I am not sure. I think several questions come to my mind, and one is with regard to the overall assessment of male-to-female ratio for this type of

cancer.

Let me make a few general statements before I comment on that specifically. One is, I haven't had a chance to see this paper before, and I note that they have a higher percentage of lung cancers that they attribute to bronchioloalveolar carcinoma than what I have previously said here. The diagnosis of bronchioloalveolar carcinoma and the classification of a tumor as bronchioloalveolar carcinoma is not always agreed upon by all pathologists.

Some tumors have exclusively a bronchoalveolar type of architecture. These tumors I think all pathologists would call bronchioloalveolar carcinoma. A large number of adenocarcinomas have a portion of the tumor with a bronchoalveolar pattern. Some pathologists call those adenocarcinomas with bronchoalveolar features. Other pathologists will call those bronchoalveolar carcinomas.

Q Let me just jump in for a moment, you can complete your answer, but isn't it the standard in pathology and in recognizing the fact, and you have

mentioned this earlier, that you can see mixed types of cancer in the lung, for instance, you can see some evidence perhaps of adenocarcinoma, you can see some evidence of a squamous cell differentiation, but the real standard in pathology ordinarily is that you make the call of cell type based upon the predominant cell type apparent in viewing the pathology specimen; is that correct?

A That is not always the standard. It is sometimes the standard. For bronchioloalveolar carcinoma and adenocarcinoma, a tumor may have a central nidus where there is a solid tumor and is what one would call an adenocarcinoma, and a larger peripheral region where there is spread of tumor cells along preexisting alveolar walls, that is a bronchoalveolar pattern. A large number of pathologists, including myself, would still classify those as adenocarcinomas with bronchoalveolar features rather than as a straightforward bronchioloalveolar carcinoma.

It is not clear to me what the authors have

used for their criteria. In fact, they make some references to point out that there are differences with regard to the diagnosis here.

Q Doctor, let me just jump in for a moment. I direct your attention to the top of page 2379, you see on table 1, they have set out diagnostic criteria for bronchioloalveolar carcinoma.

Are those the criteria that you use in making a diagnosis of bronchioloalveolar carcinoma?

A Those are criteria that I would use. I would be very surprised if using those criteria that one would come up to a percentage of 14.7 percent of all tumors.

Q Actually, Doctor, look at page 2378, in the first partial paragraph on that page, last sentence, reading BAC -- in all caps -- which is bronchioloalveolar carcinoma, increased from 5.0 percent of cases in the 1955 to 1960 cohort to 24.0 percent of the 1986 to 1990 cases.

So the question is, Doctor, the current figure that is being reported by Drs. Barkley and

Green for the percentage of all cancers that are bronchioloalveolar carcinoma of the lung is actually 24.0 percent; isn't that correct?

A That is what they are reporting. I would be very surprised and I would really want to see more of that data. They are referencing some other work.

Q You would agree, wouldn't you, Doctor, that 0.5 percent of all lung cancers as you have described the portion constituting BAC, or bronchioloalveolar carcinoma, is a pretty significant departure from the data that Drs. Barkley and Green are reporting at 24 percent?

A Yes, sir, it is. I would be very surprised to see such a high percentage. In my own experience of looking at cases of lung cancer at Johns Hopkins, I can say with confidence that we do not see anywhere near 24 percent of lung cancers as bronchoalveolar carcinomas.

Q Doctor, I know you haven't had a chance to review this entire article, but there's some particular language here that I would like to ask you

about.

On page 2383 of Exhibit No. 13, in the middle of the page, there is a paragraph beginning in conclusion. Would you read that to yourself down about, say, 10, 15 lines, and then I will ask you a couple questions.

A (Witness complying.)

Q Let me just read from the top of that paragraph.

In conclusion, several large series have documented a dramatic increase in the incidence of adenocarcinoma of the lung. An increase in bronchioloalveolar carcinoma appears to be responsible. Patients with BAC -- all caps -- are younger at the time of diagnosis, more likely to be female, and less likely to be current or former heavy smokers when compared with patients with other types of NSCLC -- in all caps -- including nonbronchioloalveolar adenocarcinoma of the lung. The etiology of BAC -- all caps -- is uncertain.

Do you agree or disagree with the language

that I have just read?

A I hesitate to agree because, again, from the work that I have read and from my own experience I have seen a much lower incidence of bronchioloalveolar carcinoma than what these authors are reporting. In fact, traditionally bronchioloalveolar carcinoma has been described as a disease most commonly in men, and in middle-aged men. This is very different than other information that has been published, and I have a hard time commenting on it until I have a chance to look at it some more.

Q Doctor, to the extent that you have been able to scan this article during our discussion of it and by looking at the front page of the article, you recognize that this is actually not original research but it is a review article --

A Yes.

Q -- is that correct?

So that what is being reported by Drs. Barkley and Green in this article entitled Bronchioloalveolar Carcinoma is actually the

compilation of research that they have obtained through their own library efforts in understanding bronchioloalveolar carcinoma; is that correct?

A Yes, sir.

Q Okay. So this is not new scientific information, it is in fact existing reported studies that both Drs. Barkley and Green have summarized here and provided some of the most recent incidence data available; is that correct?

A Yes, sir, but that also makes it even more surprising that some of their conclusions are so different than other recently published review-type material.

For example, the Armed Forces Institute of Pathology Fasicle on lung cancer would report a much lower incidence of bronchioloalveolar carcinoma.

Q You said you had some familiarity with a Dr. Mark Green as a clinical oncologist?

A I am not sure that it is the same Mark Green, and in fact I note here that this Mark -- well, it is possible that it's the same Mark Green. I don't

know.

Q Are you aware that Dr. Mark Green has been listed as an expert in the field of oncology by the plaintiffs in this matter?

A No, sir, I am not.

Q Maybe for clarification of the record I should note that Exhibit No. 13 is entitled Bronchioloalveolar Carcinoma, by John Barkley and Mark Green. The citation is the Journal of Clinical Oncology, Volume 14, Number 8, publication date August, 1996, pages 2377 through 2386.

Doctor, you indicated earlier that there are a number of lung cancers that have not been determined to be caused by cigarette smoking in your opinion. What other factors can be causally involved with lung cancer?

MR. PATRICK: I am going to object to the question because I think it is an improper statement to prior testimony, but you can answer.

A There have been other agents that have contributed to being causes of lung cancer including

asbestos, radiation injury, certain heavy metals including nickel, cadmium, aromatic hydrocarbons resulting from industrial exposures, and then there are cases of lung cancer for which no cause can be determined.

Q Is radon a cause of lung cancer?

A It probably is. There are some epidemiologic studies that have indicated that there would be difficulty in implicating radon as a cause of specific lung cancers, but I would say that in general radon does cause some lung cancers.

Q Is bischloromethylether a cause of lung cancer?

A Yes, sir.

Q Is acrylonitrile a cause of lung cancer?

A Yes, sir, I believe it is.

Q Is beryllium a cause of lung cancer?

A I don't recall beryllium as being a cause of lung cancer. Beryllium can cause a condition known as berylliosis. There may have been an epidemiologic link also with beryllium and lung cancer. It's kind

of a moot point because I don't think anybody in the United States has been exposed occupationally to beryllium for a long long time.

Q Is silicosis a cause of lung cancer?

A I do not believe the evidence is sufficient to implicate silica as a cause of lung cancer. The process silicosis is a process of fibrosis, I do not believe that fibrosis is a cause of lung cancer, so that this other disease process, the fibrosis certainly is not a cause of lung cancer, I do not believe that there's sufficient evidence to implicate silica as a cause of lung cancer.

Q Are you familiar with the term scar cancer, Doctor?

A Yes, sir, I am familiar with that term.

Q What is the definition of the term scar cancer?

A That is a term that is not commonly used in pathology now. I think that it is a term that was commonly used before my time of training in pathology. It refers to cancers that are thought to originate

in scars, primarily scars from tuberculosis.

Q Are you familiar with the particular cell type that is involved with a scar cancer?

A Most scar cancers are adenocarcinomas, and again, formerly it was thought that these cancers arose in scars, particularly from tuberculosis. There is well-recognized a problem with that logic in that adenocarcinomas generate scarring as a result of the cancer, so when a pathologist evaluates the cancer and sees scarring, it is very likely that the scarring was secondary to the cancer rather than the cancer arising in the preexisting environment of the scar. I think that is recognized now because tuberculosis scars are so uncommon, and there's good clinical documentation of adenocarcinomas that arise in lungs that don't have preexisting scars.

Q This fibrotic development after the observation of a lung cancer in a particular location in the lung, is that regarded as a desmoplastic reaction?

A Yes, sir, I think it is fair to use that

term.

Q Is it somewhat controversial in the field of lung cancer research as to whether or not scar cancers indeed are the result of a scar etiology?

A No, sir. I, in fact, have witnessed no controversy, no arguing. I interact a lot with people who do lung cancer research, and I am not aware of anybody that believes that the cancer arises from the scar.

Q So currently what might have been regarded as a scar cancer in the last 15 or 20 years would not be believed to be a cancer that had the scarring of the lung as part of its etiology?

A In most cases, no. I have not carefully examined all of the old literature on tuberculosis and cancers, and it is possible that tuberculosis injury could result in a situation where there would be a promotion of growth of cells in a local environment where there is a scar and therefore there could be an increased incidence of cancers in the location of the scar, but I am not aware of anybody who currently

believes that the scar in itself causes the cancer.

Q So no controversy, it's a foregone conclusion these days, a scar does not cause lung cancer?

A In my opinion there is no controversy in that area. I am not aware of any scientist studying lung carcinogenesis who would argue that the scar itself causes the cancer.

Q Even if a scar is observed as a preexisting condition of the lung and the lung cancer is observed subsequently to have occurred in the same area as the scar?

A Yes, sir. In such a situation I think that the current thinking would be that the same environment that led to the development of the scar also contributed to the carcinogenesis process and that they were localized to the same region of the lung. It would not be a situation where the scar caused the cancer but that the same cause contributed to the two diseases.

Q So the agent that brought about the scar

would be the cause of the lung cancer?

A In some manner, yes.

Q You mentioned tuberculosis as one source of bringing about the scar in the lung. What other factors can account for scarring of the lung?

A Well, a number of conditions can cause fibrosis of the lung. One that we are commonly made aware of is asbestos. Asbestos can cause fibrosis of the lung. Asbestos can also cause lung cancer.

Q Can a scarring caused by asbestos be a condition that brings about a later-appearing carcinoma of the lung?

A No, sir. In my opinion the scarring itself does not cause the cancer.

Q So the scarring itself resulting from something like asbestos or tuberculosis you believe has no role in the actual occurrence of the lung cancer associated with the scar?

A That is correct.

Q So in the instance of tuberculosis, you believe tuberculosis to be a cause of lung cancer?

A That I don't know because I have not examined epidemiologic data relating to tuberculosis and lung cancer incidence. I don't know if there is such data, if the investigators considered confounding factors such as cigarette smoking.

I am aware of references really before my medical training to scar cancers that were specifically referencing cancers that arose in tuberculosis scars. Again, that's not something we deal with currently because tuberculosis scars are very uncommon in the United States in the second half of this century.

Q So you don't know what accounts for the cancer that would arise in association with a scar known to be part of a preexisting condition of tuberculosis?

A Correct. And I am not even sure that there is a statistical association between tuberculosis and lung cancer. I don't know that that exists.

Q Can scarring occur in the lungs as a result of recurrent bouts of pneumonia?

A Yes, sir, it can.

Q Can scarring occur in the lung as a result of a condition of scleroderma?

A Yes, sir.

Q Any other illnesses that can result in scarring of the lung?

A Rheumatoid arthritis can result in scarring of the lung, and this is an idiopathic condition whereby scarring of the lung develops without any obvious etiology.

Q Can trauma to the lung result in scarring?

A Yes, sir, that most likely would be localized to the region of trauma.

Q Doctor, do you know whether air pollution is a contributory factor in development of lung cancer?

A There have been many studies that have tried to make such an association, and such an association, if it exists, is probably not terribly strong.

Air pollution means different things in

different areas, some air pollution does contain polycyclic aromatic hydrocarbons, particularly urban pollution involving combustion exhaust. These compounds are carcinogenic to the lung, and it appears logical that epidemiologic studies that would show a higher incidence of lung cancer in groups of people with this type of exposure if they have accounted for confounding factors such as cigarette smoking, that there would be some reason to believe that the air pollution does contribute to the lung cancer.

Q Are you familiar with research that points to dietary factors as contributing factors in causation of lung cancer?

A I am aware of a lot of attempts to link dietary factors, and I cannot recall any specific link that stands out.

I know particularly that investigators had been looking for a particular vitamin, for example, where high levels of intake would be associated with protection, and from my recollection I don't think that any such link has been found.

Q Do you agree, Doctor, that in nonsmoking women the most common cell type of lung cancer is adenocarcinoma of the lung?

A Yes, sir.

Q Are you familiar with a study in, I think it originated in Missouri, that studied the effect of high fat diet on the incidence of lung cancer in women?

A I am not aware of that study.

Q Would you be surprised to know that a relative risk of 11 was established for the association between a high fat diet and the incidence of adenocarcinoma in women?

MR. PATRICK: Objection to form.

A I guess for something like that I would have to see the study and have a chance to look at it and I could comment on it. It would surprise me if the only factor involved, the only risk factor involved for adenocarcinoma in nonsmoking women was a high fat diet.

Q Well, my question really relates to not the

idea that we are establishing this as a sole factor in the incidence of lung cancer in women. It's the idea that it's at least a factor that has been associated with adenocarcinoma in women to the extent of a relative risk calculation of 11.

A I would be surprised if it were so high. If you have that data, I would like to review it.

Q Are you familiar with any data that associates alcohol consumption with lung cancer, Doctor?

A I am sure there is, and that's very difficult to assess such a study because alcohol consumption is often accompanied by cigarette smoking, whereas the converse is not always true.

I have not reviewed such studies, so I would have a difficult time commenting on them.

Q Is diesel exhaust a cause of lung cancer?

A I am aware of studies that have linked high exposure to diesel exhaust and increased incidence of lung cancer, and in my opinion exposure to high levels of diesel exhaust can contribute to the development of

lung cancer.

Q It is fair to say, isn't it, Doctor, that lung cancer is a multifactorial disease?

A What do you want to say, that the cause of lung cancer is multifactorial or that -- rather than lung cancer is a multifactorial disease?

MR. PATRICK: Maybe I should object to the question.

Q Maybe you can take it two different ways.

A When you say lung cancer is a multifactorial disease, it is a little more ambiguous, I don't know which direction you are referring to. If you are referring to the different factors of causation, if you are referring to the different factors that go into the diagnosis, if you are referring to the different factors related to behavior of the disease.

Q So in any one of those respects, it would be regarded as multifactorial. Is that fair?

A I would have a hard time disagreeing with you, being so late in the afternoon. Almost every

disease has some level of complexity, even ingrown toenails. Ingrown toenails are multifactorial diseases, there's a level of complexity to that. Virtually every disease has some level of complexity.

Q Any molecular biological examination of ingrown toenails, Doctor?

A Not that I am aware of. I don't think that anybody would fund it. If I were on a study section, I certainly wouldn't give a lot of credit to such a study.

Q Doctor, you mentioned earlier at least one of the categories of information that you might examine in making some determination of a cause and effect relationship between a factor and a disease would be animal studies.

A Yes, sir. That's one area that we looked at.

Q What type of animal studies were you referring to?

A With respect to lung cancer?

Q Yes.

A Well, there have really been a whole host of animal studies, and there are many more animal studies that have been conducted than I am aware of.

There have been animal studies that have been conducted involving inhalation models where animals were forced to inhale cigarette smoke. There have been animal studies conducted where animals were exposed to components of tobacco smoke. There are in vitro studies using animal cells where animal cells have been exposed in culture to components of tobacco smoke. There's a wide range of studies, a large number of studies; I am certainly not familiar with all of them.

Q To the extent that you are familiar with animal studies involving the inhalation of tobacco smoke, what have those studies shown?

A Well, it varies by species. First of all, it is very difficult to conduct inhalation studies because animals do not voluntarily breathe tobacco smoke. Rats or mice are small animals, choke and gag and do everything they can to not inhale the smoke.

There have been some studies conducted with beagles where they were kind of forced to smoke through a tracheostomy. I am sure that there have been inhalation studies where rats or mice were put into cages where they inhaled tobacco smoke. I know there have been such studies. And then there are also studies, as I have said, where animals have been exposed to components of cigarette smoke.

Q Yes. My question relates to what was demonstrated by the studies involving the inhalation of tobacco smoke.

A Well, in most of those studies, the end result was that animals that inhaled the cigarette smoke eventually developed pulmonary neoplasms, either pulmonary adenomas or pulmonary adenocarcinomas or some type of small -- at least a small pulmonary neoplasm, if not a fully developed cancerous tumor.

Q Were these studies regarded as positive animal studies establishing animal models for the production of lung cancers due to the inhalation of tobacco smoke?

A I don't know. I think there is probably a mixed reaction. I think there was probably disappointment that the model did not exactly mimic human cancer. That's not surprising because animal models of most diseases don't commonly mimic the human disease. It is very difficult to get a good animal model of a human disease.

I think that they were positive in establishing that the cigarette smoke components were tumorigenic. The tumors may not have been the same types of tumors that a pathologist or clinician would observe in humans, but again, as I have said, these models often do not exactly mimic the human situation.

It is very difficult to find animal models for human breast cancer. It is very difficult to find animal models for other types of human cancers, simply because animals don't develop the same types of cancers that humans do.

Q Okay.

Without regard to whether it was the same type of cancer that a human develops, were these

inhalation studies, at least some of them, reporting statistically significant increases in the production of lung cancer in these animals as a result of the inhalation of tobacco smoke?

A Yes, sir, they demonstrated that the animals developed lung tumors as a result of inhalation of tobacco smoke.

Q Just for clarification, your reference to lung tumors is equivalent to saying lung cancer?

A Some of the lung tumors did not have all of the invasive and metastatic properties that human lung cancer has. That's why I am using the term tumor rather than cancer. They were certainly neoplastic processes in the lung. They were certainly growing in an abnormal manner.

Q Is it your opinion that a benign tumor is the same as a malignant tumor?

A No, sir, they are not. These animal tumors were not analogous to benign human tumors either, and I think it is probably not fair to call the neoplasia that occurs in animals after exposure to cigarette

smoke a benign process. It is not exactly analogous to human malignancy, but it is certainly a neoplastic process.

Q So what can you really conclude from the animal studies that involve the inhalation of tobacco smoke with respect to human pathology?

A I think it demonstrates that the cigarette smoke components are capable of inducing a neoplasm of the respiratory system. Maybe that seems like something that's totally logical just because if you expose the human bronchial tract to carcinogens, you would expect neoplasms to arise, and in fact that is entirely logical. This is just establishing that that is true, exposing the respiratory system to these particular agents causes neoplastic transformation of cells that are so exposed in vivo.

Q So it is your impression that the scientific community regards the inhalation of tobacco smoke in animals, those studies, as being studies that support the idea that cigarette smoking causes lung cancer?

A I think it gives support, yes. I don't think it is a critical element. I think there are so many elements in our understanding here that no one element is entirely relied upon.

Q Do you know whether the Surgeon General of the United States has ever recognized that inhalation studies in animals has successfully produced cancers in the lungs of animals?

A I don't recall exactly how the Surgeon General interpreted that data. I have to go back and look at that.

(A short break was taken.)

BY MR KEMNA:

Q Doctor, your involvement in litigation, specifically the asbestos litigation, has involved your participation as an expert witness in your field of expertise, that being pathology; is that correct?

A Yes, sir.

Q And in the context of those cases, you have been in a position that you have expressed an expert opinion as to the causation of cancer in those cases;

is that correct?

A Yes, sir.

Q And specifically cancer of the lung; is that correct?

A Cancer of the lung and mesothelioma.

Q So that in the context of those cases you reviewed medical records with respect to individual plaintiffs and made your assessment on an individual basis what was the cause of their lung cancer, if it was lung cancer?

A Yes, sir, based on my examination of the medical records and pathology materials.

Q I take it with respect to the smoking and health litigation, of which this case is one, you feel that you are in a position to, on an individual-by-individual basis, make a determination of the cause of lung cancer in those individuals that may be part of the consideration in this lawsuit.

MR. PATRICK: I am going to object.

A I would assume that if I were to see case by case, I could for most cases express some opinion.

Q And the basis for you attempting to express an opinion as to each individual's cause of their lung cancer would be based, at least in part, on your examination of pathology materials that may be available on those individuals; is that correct?

A Well, that would certainly be important for asbestos-related cancers in the situations where there is no documentation of other asbestos-related diseases from a clinical criteria.

In a situation such as looking at lung cancer on a case-by-case basis trying to determine whether or not it was caused by cigarette smoking, I think the only contribution of a pathological examination would be to make a diagnosis of lung cancer which I would assume has been done already. I don't see a great need for an expert pathologist to review those materials. I don't know if it's done or it would be done on a routine basis or not, but I don't see where it's greatly needed.

Q With respect to the individual claimants, let's talk about litigation in which you have

individual-by-individual people suing a tobacco company for health-related injuries and you were to look at a particular individual within the context of that type of lawsuit. Could you arrive at a determination as to that individual, what caused their lung cancer?

MR. PATRICK: Let me object. Is this a hypothetical setting? A hypothetical question? I'm sorry --

MR. KEMNA: I think it is pretty clear in the context of the question. I am talking about an individual filing a lawsuit against the tobacco company with respect to health effects.

MR. PATRICK: All right.

THE WITNESS: If in this hypothetical situation I were asked to design an efficient legal system to deal with individual cases, I don't know that a pathologist's review of each individual case would be necessary.

BY MR. KEMNA:

Q Well, without regard to the question of

whether you think it would be necessary --

A For an efficient system, I think that the vast majority of these cases, if they are diagnosed by a board-certified pathologist, could be handled in an efficient manner without review of yet additional pathologists. It would add considerably to the cost of the whole litigation process.

Q Well, I am not really asking, Doctor, about policy with respect to litigation in this country, I am asking a much broader topic than any of us are capable of addressing in this deposition, but really all I am directing my question to is your position as a pathologist being asked by, for instance, a plaintiff's counsel in a case involving an individual filing an action against a tobacco company for what they believed to be a cigarette-caused lung cancer.

If you were asked to serve as an expert in such a case, would you be able to express an expert opinion with regard to an individual's cause of lung cancer in such a case?

A Yes, I would. I don't know what unique

perspective I could bring to the process as a pathologist, assuming that the diagnosis of lung cancer has already been made by a qualified pathologist. The opinions that I would express would be based on the general medical understanding of tobacco smoke as a cause of lung cancer. I can confirm the diagnosis as a pathologist, but beyond that the link between cigarette smoking and lung cancer can be done by other individuals other than a pathologist. You do not need a pathologist to say that.

Q Okay. And I understand what you are saying, you don't need a pathologist to arrive at that conclusion, but a pathologist can express an opinion on the causation of an individual's lung cancer based upon a review of the records and a review of the pathology specimens available in such a case; is that correct?

A A pathologist could express such an opinion, yes.

Q Okay.

In fact, that is what you do in your participation in asbestos litigation, is, from a pathologist point of view, express an expert opinion as to the causation of individuals' lung cancer in context of that litigation; is that correct?

A Yes, sir. That is correct. I would have to add that in some situations I don't understand fully what unique perspective I bring to the case and why a pathologist's participation in the whole process is necessary.

Q Doctor, you talked earlier about a so-called fingerprint of identifiable changes on the molecular level that you would associate with a cigarette smoking etiology. What is composed of such a, quote unquote, fingerprint?

A There are certain genetic alterations that are very closely linked to a specific carcinogen exposure, namely, the G to T mutation of the p53 gene in lung cancer at specific mutational hotspots. That, I think, is one example of a mutation that is very closely linked to a specific carcinogen exposure, and

that is an example of what people in molecular oncology are now calling a fingerprint for a specific mutational or exposure causing the cancer.

Q What specific carcinogen are you referring to that results in a G to T mutation?

A Benzpyrene.

Q For the record, I have had marked as deposition exhibits sequentially numbered from 4 through 12 the contents of Dr. Gabrielson's file that he has produced at the deposition of today in response to the request for production of documents in the notice of deposition.

I am going to show you what's been marked as Deposition Exhibit No. 7 which is one of the documents that you produced here today.

Doctor, that article that I just handed you, Exhibit No. 7, is entitled Preferential Formation of Benzo-a-pyrene Adducts at Lung Cancer Mutational Hotspots in p53, published in Science on October 18th of 1996.

Is this article representative of the

information that you are referring to with respect to benzo-a-pyrene and mutational hotspots in p53?

A Yes, sir, I would say so. There have been other articles that have demonstrated benzo-a-pyrene to cause mutations in p53 in vitro systems. This is one of the articles in a series of articles related to that topic, and this specifically deals with the formation of adducts at specific nucleotides in the p53 molecule.

Q Are you telling me that this article is not telling us anything new?

A It does tell us some new things.

Q Okay. What is it that's new about the findings reported in this article?

A This article demonstrates that benzpyrene adducts do not occur randomly on the p53 molecule but that they occur specifically at the mutational hotspots, which are guanine positions and codons 157, 248 and 273.

Q Hasn't that been recognized previously?

A No, sir.

Q So this is the first time that it's been recognized that benzo-a-pyrene actually binds to areas of the p53 gene of DNA that represents the same areas recognized as mutational hotspots?

A Let me explain a little bit more.

It has been recognized that there are certain mutational hotspots, certain nucleotides of the p53 gene, that are commonly altered in cancers. With respect to lung cancer, these three mutational hotspots are commonly observed, and for lung cancer one of the mutational hotspots appears to be unique or relatively unique for lung cancer in that it is not seen in other types of cancers. It has been found that benzpyrene can cause G to T mutations, which are the types of mutations that are seen at these specific regions of the p53 gene.

The question that I saw this paper addressing is whether or not benzpyrene causes adducts randomly throughout the p53 gene and subsequently induces mutations randomly through the p53 gene and only specific mutations are selected for on a cellular

level, or whether at the earlier stage there is a preferential targeting for these mutational hotspots by the carcinogen.

It turned out that in fact there was a preferential targeting for these specific nucleotides by the carcinogen.

Q This article doesn't demonstrate that benzo-a-pyrene actually results in the development of mutations at these hotspots of p53, does it?

A I think that that's really been demonstrated in other work. I don't think that this article specifically addressed that.

Let me qualify that again. I think that other work has demonstrated that benzpyrene binds to DNA and causes the G to T mutation. This article is again specifically addressing whether that occurs randomly throughout the p53 gene and that only certain mutations have a growth advantage for cells, or whether these mutations are targeted to specific areas.

Q Okay. Let's break this down a bit, Doctor.

When you talk about benzo-a-pyrene reacting with the DNA in the regions of hotspots for p53 mutations, you are talking about something on the front end where a benzo-a-pyrene molecule comes in and binds to an area on the nucleotide chain of the DNA molecule; is that accurate?

A I think that is reasonable, yes.

Q That is called an adduct, isn't it, Doctor?

A Yes, sir.

Q So you know that the benzo-a-pyrene may have some affinity for certain spots on the DNA molecule with respect to certain nucleotides at certain numbered positions that are reported in this article?

A Yes, sir.

Q The other part of the story that we have some information on is that with respect to actual mutations of p53 that you can recognize certain characteristic mutations, certain areas of the p53 molecule, that seem to be represented by changes in nucleotides as you have described a G to T mutation;

is that correct?

A Yes, sir.

Q Okay.

Are you saying that this article demonstrates that benzo-a-pyrene binds to a particular hotspot region of the DNA molecule and they have followed the process such that they can make a direct link between the binding on the DNA molecule as an adduct and the actual production of the mutation in the DNA on the back end of the process?

A In fact, I am not aware of this study following that to the point of recognizing the mutation to the thymidine nucleotide from the guanidine.

Q Excuse me for a second. Just to clarify, when you refer to G, you are referring to guanidine?

A The T refers to thymidine.

Again, I don't think in this study that they followed it through to that point. I could reread it, but I don't recall that piece of data here. That is some preexisting knowledge in the scientific

community that, first of all, benzpyrene does bind to guanine. Guanine -- it should be called guanine, not guanidine -- binds to guanidine.

Also, it is known prior to this study that benzpyrene causes a transversion mutation from guanine to adenine. That is known prior to this study.

This study specifically is directed at determining where the binding occurs, whether it is random in the p53 molecule or if it's directed to these mutational hotspots.

Q Okay.

Is benzo-a-pyrene the only substance that has ever been associated with G to T transversion mutations or G to A transition mutations?

A G to A transition mutations I believe are commonly associated with ionizing irradiation. G to T transversions have also been described after exposure to oxygen-free radicals and perhaps others, so that the G to T transversion is not unique for benzo-a-pyrene.

Q So there are any number of substances that

might bring about a G to T mutation on p53?

A That may be an overstatement to say there are any number of such substances. I am aware of oxygen radicals and benzo-a-pyrene. There may be others, but I am not aware of other substances that caused that type of mutation.

Q There's a lot yet to be determined, isn't there, Doctor, with regard to what types of substances might actually result in the G to T mutation on p53 gene?

A Well, perhaps, but this article is starting to point out positional preferences, and when you take that in context of what's already been recognized for lung cancer the mutational hotspots, particularly for lung cancer having one mutational hotspot that's not seen in other types of cancers, then going one step further and having this link between a common carcinogen for lung cancer, namely benzpyrene, having an adduct at this specific mutational hotspot and causing the specific mutational change that is observed in lung cancer, that is a very strong link of

a chain of events there. I think it would be unreasonable to say that any number of substances could cause this because in fact we don't see these types of mutations in other types of cancers, other than lung cancers, specifically referring to one mutational hotspot. We don't --

Q Hold on just a moment.

What mutational hotspot are you saying is specific only to lung cancer?

A I believe it is codon 157, I would have to double-check that, which I think is in exon 7. I am not going to say it is specific only to lung cancer, but I believe that is rarely observed, if ever, in other types of cancers.

Again, I would have to review that for sure, but there's one of these hotspots that is unique to lung cancer.

Q Can we say definitively that only benzo-a-pyrene can produce a mutation at codon 157 of p53?

A A G to T transversion in codon 157 of the

p53 gene? I don't think that that can be said definitively, but I think that there is strong evidence linking that agent to the predominant -- most mutations of that nature that exists in people, because it is limited to a certain type of cancer, a certain type of cancer that's observed in smokers as opposed to nonsmokers.

Q Doctor, how often does p53 mutation occur in lung cancer?

MR. PATRICK: I'm sorry. Were you finished with your earlier answer?

THE WITNESS: I don't even remember what the earlier answer was at this point.

MR. PATRICK: Okay. Go ahead. I'm sorry.

A Approximately 60 percent of all lung cancers have p53 mutations.

Q Okay.

Doctor, we can conclude from that that p53 is not a necessary step in terms of genetic process for bringing about lung cancer then; is that correct?

A It appears that mutation of p53 is not

necessary for the development of lung cancer. There are other pathways for the development of lung cancer.

Q Okay.

And in fact it is not even present in upwards of 40 percent of lung cancers; is that correct?

A Yes, sir.

Q How do you know which lung cancers requires p53 and which ones don't?

A There's really no way of telling which lung cancers have mutations of p53 and which ones don't without direct sequence analysis of the p53 gene in tumors.

Q It is true, isn't it, Doctor, that in fact with any cell type of lung cancer there is no one-to-one relationship between the presentation of lung cancer and by tissue analysis the presence of p53 mutation?

A That is correct for small-cell lung cancer. Eighty to 90 percent of the tumors have p53 mutations.

Q Isn't it true, Doctor, that p53 mutations

occur in cancers at other sites in the body?
A Yes, sir, that is true.
Q And what other sites in the body do p53 mutations occur?
A Many other tumors. Bladder cancers, some breast cancers, colon cancers, other common epithelial tumors, brain cancers.
Q And isn't it true also, Doctor, that G to T transversion mutations of p53 occur in many other cancers outside the lung?
A Less commonly than they do in the lung.
Q Now, you have mentioned breast cancer as one type of cancer where you can observe p53 mutation.
G to T transversion mutations occur in breast cancer tissue?
A Yes, they can, but my recollection is that it is much less common than in the lung, and furthermore the overall incidence of p53 mutations in breast cancer is much lower than the overall incidence of p53 mutations in lung cancer.
Q Does p53 mutation in breast cancer have

anything to do with the mechanism of carcinogenesis of breast cancer?

A It most likely does, yes, sir.

Q Is breast cancer thought to be caused by cigarette smoking?

A I don't think of breast cancer as being caused by cigarette smoking.

Q Colon cancer, where p53 mutations can be observed, can you see G to T transversion mutations in colon cancer?

A Yes, sir. Again, those G to T transversions are less common than they are in lung cancer.

Q Is colon cancer caused by cigarette smoking?

A In my opinion, colon cancer is not caused by cigarette smoking.

Q So it is pretty clear, isn't it, Doctor, that the mutation of p53, and more specifically within the p53 gene the G to T transversion mutation, is not necessarily part of a cigarette smoking etiology for

carcinogenesis?

MR. PATRICK: Objection to form.

A A G to T transversion at one of these mutational hotspots in a lung cancer is more likely than not related to cigarette smoking. In general, not all G to T transversions at other places of p53 mutations and other types of cancers are related to cigarette smoking.

Q How do we know that p53 mutations really have anything to do with the process of carcinogenesis in the lung?

A There have been to my knowledge few direct experiments relating to replacing lung cancer cells with an intact p53 gene. There have been experiments done with other cell types that have cancerous cell types with mutated p53 and replacing a normal p53 gene and finding a loss of the tumorigenic phenotype. In fact, that evidence is so compelling that p53 is a tumor suppressor gene and is involved in suppression of cancer, one could not get funding for a proposed project to do that specifically with lung cancer

cells.

Other evidence that it is important in lung cancer come from studies of a very rare familial condition, Li-Fraumeni disease. These are families with inherited p53 mutations. Again, it is a very rare disease, but these families have been found to have increased incidences of lung cancer.

In the scientific community, I don't think that there would be any significant doubt that p53 mutations in lung cancer are an important component of the malignant phenotype for that tumor.

Q Is mutation of p53 sufficient in and of itself to bring about lung cancer?

A No, sir.

Q We have already determined that it is not a necessary step in the development of lung cancer, but how many other mutational steps or other molecular biological phenomena are involved in bringing about lung cancer?

A I think reasonable estimates now are that there are ten, or perhaps more, mutational events that

are required for the full malignant transformation of any human cell, whether it be a colon cell, a lung cell, a breast cell, and that is largely based on our recognition of how many genetic abnormalities are likely to be present in existing cancers.

Q Is there more to be discovered with regard to what types of steps are required to bring about cancer of the lung?

A At this time I think that there's a pretty good understanding with regard to the precancerous conditions from a morphological standpoint, I think that there is a good conceptual understanding of multiple steps of carcinogenesis both from the perspective of multiple carcinogenic exposures causing the cancer as well as multiple mutations being required to transform the cell into being fully malignant. All of the genetic alterations that are important for lung cancer have not yet been identified.

Q So you have reason to expect that you could get further funding if you were to submit proposals

for research in this area?

A Yes, sir. If one were to submit a proposal attempting to identify a tumor suppressor gene for a lung cancer or an amplified gene for lung cancer, that would be an area that one could be hopeful of getting funding for.

Q How many different oncogenes have been identified in the investigation of carcinogenesis for lung cancer?

A I don't know the number off the top of my head. Ras mutations have been described in lung cancers. Amplifications of genes in the myc family, m-y-c, have been described for lung cancers. I am not really aware of any other oncogene changes that have been commonly described.

I should preface this by saying that when I am discussing oncogenes, I am referring only to a set of genes that are considered to be genes that positively influence a cell toward the malignant phenotype rather than the tumor suppressor genes when their presence inhibits the tumorigenicity of a cell.

Q I appreciate that clarification.

Are you familiar with the raf, r-a-f, oncogene?

A Yes, sir.

Q Is that believed to be at least relevant to carcinogenesis of lung cancer?

A Yes, sir. There are some alterations of raf in some lung cancers.

Q Are you familiar with the fur, f-u-r, oncogene?

A I have heard of the fur oncogene, yes, there have been descriptions of some fur mutations in lung cancers less commonly than alterations of some of the other genes.

Q Are you familiar with the jun, j-u-n, oncogene?

A Yes, sir. I am aware of alterations in levels of jun expression in different types of cancers. I may have missed it, but I am not aware of any primary mutational changes of the jun oncogene in lung cancer.

Q Doctor, how many tumor suppressor genes have been identified as significant in the carcinogenesis process?

A For lung cancer?

Q For lung cancer, yes.

A I will try to list them. The p53 gene, the rb gene, the MTS p16 gene. I think those are the major tumor suppressor genes that have been commonly found to be altered in lung cancer.

Q Any other genes that you can remember, whether commonly or not, found to be altered in lung cancer?

A There have been, I believe, rare cases where alterations of the DPC4 gene. I can't really recall any others that have been described.

Q Let's just for clarification line up the identification of the suppressor genes that you have mentioned with their chromosome location.

The p53 gene that you are referring to relates to chromosome number 17 --

A Yes, sir.

Q -- is that correct?

When they talk about mutational change, or, as you have referred to it before, allelic loss --

A Those are actually two different concepts.

Q Okay.

A Inactivation of a tumor suppressor gene requires biallelic inactivation. Usually that's accompanied by a mutation of one allelic copy of the gene and loss of the corresponding normal allele by some chromosomal mechanism.

Q That operates with respect to chromosome 17 when you are talking about the inactivation of the p53 tumor suppressor gene; is that correct?

A Yes, sir.

Most commonly inactivation of p53 gene occurs by a mutation of one copy of the p53 gene and loss of the corresponding normal allele.

The rb gene is another one that I mentioned, which is on chromosome 13.

Q The MTS gene, suppressor gene that you referred to is on chromosome 9?

A Yes, sir, 9p.

Q Okay.

Is there also a tumor suppressor gene associated with the locus on chromosome 9q?

A There is a tumor suppressor gene. BRCA1 gene is on chromosome 9q. I am not aware of any linkage of that gene to lung cancer, although I would not be surprised if individual cases have been reported with BRCA1 mutations.

There very likely are other tumor suppressor genes on 9q that have not yet been identified. In fact, there are some candidate genes that have been considered, the prohibitin family has one or two genes on chromosome 9q that have been considered to be tumor suppressor genes, but no specific gene on 9q has yet been demonstrated to be a tumor suppressor gene other than the BRCA1 gene.

Q Is there a tumor suppressor gene --

A I'm sorry, BRCA1 is on 17q, not 9q. It is getting late in the day.

MR. PATRICK: I have to make a quick phone

call. Take me one minute.

(A short break was taken.)

BY MR. KEMNA:

Q Doctor, are there tumor suppressor genes, gene or genes, that have been identified at the locus of chromosome 6q?

A No. That is something that we are trying to do.

Q Okay.

Are there tumor suppressor genes that have been identified at chromosome 6p?

A No, sir. I don't think that that's particularly a hotspot. There may be a tumor suppressor gene there, but I think most loss of chromosome 6 is related to a suppressor gene on 6q.

Q Is there a suppressor gene identified at chromosome 5q?

A The DPC or DCC gene relating to colon cancer. I am not aware of any lung cancer genes that are on chromosome 5.

Q Are you familiar with any allelic loss on

chromosome 5q that is observable in small-cell lung cancer?

A I don't recall that being a major area for small-cell lung cancer. Most consistent allelic loss is on chromosome 3p where there has also been observed to be a number of homozygous deletions. For efforts to identify lung cancer suppressor genes, that is the focus of an intensive effort, to find the suppressor gene on 3p.

Q So they are still looking on 3p for a tumor suppressor gene?

A Yes, sir.

Q And the mutational activity that they observe on 3p leads to some suspicion of a tumor suppressor gene?

A There is compelling evidence that there is an important tumor suppressor gene on chromosome 3p that is involved in many types of cancer. It is likely that it is the same gene involved in many types of cancer, it could be different genes for lung cancer than for other types of cancer, but it is likely to be

the same gene.

Much of that evidence comes from study of small-cell lung cancer where I think probably every small-cell lung cancer that has ever been looked at has at least allelic loss involving this region of 3p, and there are many small-cell lung cancers with homozygous loss.

Q Are there any tumor suppressor genes known or suspected on chromosome 2p?

A I think you can go through just about every chromosome and somebody has found what they call an increase in allelic loss.

What I think are the hotspots for lung cancer, there is something on chromosome 1, I don't know if there are genes on both 1p and 1q, but there is certainly frequent nonrandom allelic loss on chromosome 1. There is certainly frequent nonrandom allelic loss on chromosome 3p, 6q, 9p of course, chromosome 11 is commonly affected by allelic loss, and again it is not clear whether there are individual low sides for 11p and 11q.

Chromosome 17, chromosome 16, 22, chromosome 22q has frequent loss of heterozygosity in non-small-cell lung cancer. In fact, for small-cell cancer there is one study that Adrian Merlow and myself did, and I honestly forgot the different loci that he reported for small-cell lung cancer. I know that 6Q is one of them, that is the one that we have been following up on.

Q Let me interrupt you for a moment.

A He reported loss on 9p and 9q, and it appeared that there were two loci, there were two loci there, 6p and 6q were not clear, but there is a separate locus on 6p for small-cell lung cancer.

Q Okay.

All this reference to allelic loss, existence of tumor suppressor genes at all of these various locations on human chromosomes that relate to lung cancer, is information that is key to knowledge regarding the various mutations that may play a part in the etiology of lung cancer; is that correct?

A I think you have misused the word etiology

there. Etiology refers to an agent that causes disease. You probably should have used the word pathogenesis of lung cancer.

Q Let's substitute the word pathogenesis for where I used etiology, then you may answer.

A The whole purpose of trying to find these genes is to, one, better understand the pathogenesis of the disease, two, identify potential therapeutic targets that the disease can be treated.

As far as etiology is concerned, I don't see where cloning a gene on chromosome 1 and identifying it is going to help us establish what the etiology for lung cancer is. I think that's something already known.

What it may help us do is to -- particularly if we know what that gene does and how it functions -- we may be able to develop some strategies for slowing down the development of the disease, we may be able to use that as a diagnostic tool for recognizing these mutations early in smokers at high risk for developing the disease. We may find some

twists that will help us treat the disease. I don't think it is going to help us determine the etiology of the disease.

Q Okay.

In terms of talking about the pathogenesis, really understanding the series of changes that may take place in the process of carcinogenesis, these recognized areas of mutation on the various chromosomes that we have noted and the identification or suspicion of a number of tumor suppressor genes as well as the identification of oncogenes that have been identified in lung cancer, all fit into attempting to create the picture of what the actual pathogenesis on the subcellular level may be for the development of lung cancer; is that correct?

A I think that is reasonable, sure.

Q Now, considering the vast number of oncogenes and suppressor genes that we have already discussed, how do you know the extent to which individual oncogenes or suppressor genes actually participate in the production of individual lung

cancers?

A More likely than not they all participate. These are nonrandom events. It's difficult to reason that they occur and just go along for the ride, particularly if as we learn more about them we find that these changes result in cellular physiologic changes that would promote the growth of a cell, extend the doubling potential of a cell, cause phenotypic changes in a cell that are associated with a malignant phenotype. It's likely that they all have some participation in the overall process.

Q Do they all participate in each individual lung cancer?

A Well, no. It appears that there are certain critical pathways that are involved, and different cancers may have different alterations in the same pathway. A good example of that is the pathway where the rb gene product controls cell replication.

The MTS1 p16 tumor suppressor gene is an inhibitor of cyclin-dependent kinases that

phosphorylate the Rb protein, and it is probably not coincidental that for lung cancer these types of mutations appear to complement one another. Cancers with mutations or alterations of the p16 gene have normal Rb. Cancers with abnormal Rb have normal p16. These are complementary events. Both of them end up disrupting the same pathway. So I don't expect all cancers to have exactly the same mutations, but it is likely that there are certain critical pathways that will be affected one way or another in all cancers.

Q There is a lot more research necessary, Doctor, isn't there, for a confident understanding of the precise combination of oncogenes and suppressor genes that would be required to produce a lung cancer?

A I have a hard time disagreeing with you and then you turning around and telling the federal government that they need to give us support for research grants.

A lot more research needs to be done. I think we have now a great understanding of many of the important concepts of how cancers develop. We are

really getting a handle on some of the molecular mechanisms of how cells regulate replication, how these regulatory mechanisms are altered in cancers. A lot more work needs to be done, but the fact that we are understanding these concepts just opens more doors for us, more opportunities.

Q Doctor, you were talking earlier about being able to look at a specific tissue specimen and identifying a fingerprint for a cigarette smoke-caused lung cancer. What precisely do you need to see in that fingerprint, as you have described it?

A I think in your hypothetical situation is that I would be given a lung cancer specimen but would be given no history as to whether or not that person smoked cigarettes.

Q Yes. Let's start with that scenario.

A If we start with that scenario and I have absolutely no history, even in that scenario I would have to say that more likely than not, if that lung cancer is from the United States, more likely than not it was caused at least in part by cigarette smoking

just because statistically most cancers in the United States are related to cigarette smoking.

Q Let me just --

A But --

Q -- stop you temporarily there.

That doesn't rely at all then on your field of pathology to make a contribution?

A That's correct.

Now getting down to the contribution of molecular pathology. Having such a tissue, if one were to identify a p53 mutation at specific codons and these were specific G to T transversion mutations which are characteristic of the benzpyrene type of mutation, one could conclude, again, to a reasonable degree of certainty that that's the type of mutation that would be caused by cigarette smoking.

There are other possibilities, particularly for, I think it is codons 248 and 273, there are other possibilities, but again to a reasonable degree of certainty, even without any history of cigarette smoking, one could conclude that this mutation was

caused by cigarette smoking.

Q And the codon that you are referring to is 157 regarding this mutation?

A Your memory is better than mine. I have to glance down at the paper to remember the number of the codon.

I believe that 157 is the one that's unique for lung cancer. It could be one of the others, but I think it is 157.

Q So at this point all you need to see is a G to T transversion at codon 157 on p53 gene that is located on chromosome 17p?

A If I saw a G to T transversion at any of these three mutational hotspots and I had no history of cigarette smoking, I think that that would be sufficient evidence to say that that p53 mutation was more likely than not caused by cigarette smoke.

Q You are saying any one of these three mutational hotspots.

A Yes, sir.

Q Does benzo-a-pyrene only exist in tobacco

smoke?

A No, sir.

Q Where else can you find benzo-a-pyrene?

A Well, I probably cannot list all of the other places one could find benzo-a-pyrene. I am certain that it is a product of combustion of other organically-based materials, and I am sure it's present in other organically-based materials.

The important thing to remember here is that most of these other sources of benzpyrene are not directly applied to bronchial epithelial cells, whereas cigarette smoke is.

Q That's true, Doctor, but that doesn't really help you resolve whether or not the benzo-a-pyrene produced, as you would assume, benzo-a-pyrene produced mutation of p53 is specific to cigarette smoke, not knowing anything else about the individual being examined.

A I think it is reasonable for me to come to a reasonable level of conclusion. There is benzo-a-pyrene in -- there may be some in my coffee,

it is an organic compound. I would not reasonably conclude that a benzo-a-pyrene type of p53 mutation present in a bronchial epithelial cell could come from coffee, I would have a difficult time believing that someone would aspirate enough coffee and expose their bronchial epithelium to enough coffee to cause that type of change. Benzo-a-pyrene type changes in bronchial epithelium most likely comes from tobacco smoke, because that is the only situation I am aware of where people apply a great deal of benzo-a-pyrene to their bronchial epithelium.

Q I guess what you are saying, Doctor, is that your opinion with respect to causation by cigarette smoke of a lung cancer, and this is regardless of cell type, first of all comes primarily from your understanding of the epidemiological information showing an association between cigarette smoking and lung cancer, and the findings in the field of molecular biology you would find perhaps additionally supportive?

A I think that that summary kind of

underestimates what the logic here is, again going back to what we talked about this morning, what an epidemiologic study means and how you attribute some finding on epidemiologic study on causation, I think you have to look at the total logic here.

Not only do we have epidemiologic studies, not only do I have my own personal and professional observations of lung cancers occurring over and over again in smokers, let's look at the logic.

In smoking, someone is applying substances which have been demonstrated to cause tumors in animals, which have been demonstrated to cause mutations in all sorts of cell types, they are applying these directly to these cells that later develop into cancers. Now, that's analogous in my opinion to the situation of where a car crashes and drivers of a particular car are always killed in head-on collisions. In that situation I don't need to have a structural analysis of the car for me to be afraid of that car. If over and over again that type of car causes a death of the driver in head-on

collisions and other cars it doesn't occur, and knowing that car crashes with head-on collisions seem like a logical link to death of a driver, I would be willing to draw a conclusion that there is something wrong with that car that results in death of a driver. Simply the observations, clinical observations, epidemiological observations linking cigarette smoking and lung cancer as well as the very basic observation that the process of smoking involves application of these toxic and carcinogenic substances to the bronchial epithelium is enough for me to draw a logical conclusion that the smoking causes the lung cancer.

Q Doctor, you recognize that the benzo-a-pyrene inhaled in tobacco smoke is not actually what binds to a DNA molecule?

A That is true, it is metabolized to, I believe it's a benzo-a-pyrene --

(Interruption by the reporter.)

THE WITNESS: Let me see if I can find it for you in one of these articles.

They give it an even more elaborate chemical name. BPDE. It is an abbreviation, benzpyrene diaziolapoxide (phonetic).

Actually, the fact is that studies a long time ago, I believe these were done by Curt Harris and others, have shown metabolism of these precarcinogens within bronchial epithelial cells to the ultimate carcinogens. Again, even without that type of a study, that particular portion of the link, I think that there is enough evidence to establish this cause and effect relationship.

BY MR. KEMNA:

Q Doctor, don't most people live in an urban environment?

A The majority of Americans do, yes, sir.

Q Isn't it true that in an urban environment there are considerations of air pollution, automobile exhaust and so forth?

A There are. I would be shocked if you could show me any study that would find exposure levels to benzpyrene that would be parallel to those levels that

a smoker gets in terms of what the bronchial epithelial cells are actually exposed to.

Q How do you know how much it takes, Doctor, in order to result in the development of a mutation, like a mutation involving p53 at codon 157, G to T transversion?

A I don't think that there is any threshold level involved here. In fact, we all probably have mutations of our p53 genes, and we very well may each have some mutations of the specific codons of our p53 genes in our bronchial epithelial cells, but the frequency that that would occur in an urban resident resulting from urban pollution would be much much less than the frequency by which that would occur in the cells of a smoker. It would be orders of magnitude difference.

Q Doctor, how do we know at what point in the process of carcinogenesis that a p53 mutation actually takes place?

A There have been some studies that have found p53 mutations to occur in in situ cancers.

Q So that's where the cancer is already present, right?

A The cancer is already present in a form that we can recognize as neoplastic, but it is in situ and therefore has not yet begun to invade, would not be clinically recognized as cancer, so p53 mutation can be recognized in a lesion that is not clinically recognizable as a cancer.

Q That's according to your understanding of the period of time in which a cancer is expected to develop, that's pretty late in the game, isn't it?

A The in situ phase is probably relatively late in the phase, yes. We know that the p53 mutations have occurred by that stage, and they may actually occur at an earlier stage.

Q But we don't know that, do we?

A No, we don't know that.

Q How many years does it take from the point of the initial change that takes place in a cell to the point where you develop a cancer of the lung?

A Probably on the order of five to 10 years

from the time a cell is completely transformed to a malignant phenotype until it will grow to a tumor that is clinically recognized, or can be clinically recognized.

Q Isn't it true, Doctor, that mutational activity can take place in a tissue that has already been transformed into a malignant tissue and be a function of the erratic biology of a transformed cell versus a cell prior to transformation?

A Yes. It appears that cancers can continue to acquire additional genetic alterations after they are transformed and after they are already invasive cancers. There can be additional genetic changes that occur.

Q How do we know that p53 mutation is not a function of the post-transformation period where the cell is just undergoing some type of erratic genetic alterations as a function of the fact it is a transformed tissue?

A Well, there are a number of reasons. One is that, as I have said, the p53 mutations have been

found in in situ lesions, in situ cancers.

Q Let me interrupt you there, Doctor. In situ lesions, though, are transformed.

A They are not fully transformed.

Q Tissue --

A Somebody could live forever, in theory, with an in situ cancer, and in fact it is very likely that some lesions that we recognize pathologically as in situ cancers spontaneously regress. We call them in situ cancers because by cytologic criteria they appear malignant, and our concept is that this is a preinvasive lesion, but in fact these are not fully transformed cells. It is obvious that additional changes are required before those cells will invade and metastasize and result in death of the host.

Dr. Sidransky has done a number of studies in head and neck cancers which I think he has advocated, and I think appropriately, is an accessible model for respiratory cancers in general.

One of the problems with studying development of lung cancer is that the bronchus is not

readily accessible for examination and it is not easy to get people at risk for developing lung cancer to consent to undergo routine bronchoscopy and have people doing clinical research look at their bronchus on a regular basis.

It is different for the upper respiratory system where the otolaryngologist can routinely examine people and follow the development of these lesions.

In fact, p53 mutations have been found very clearly to occur before the full transformation of a cell into invasive cancer.

MR. KEMNA: Let's take a break for just a couple minutes. I will collect my thoughts and see if I can pull it together here.

(A short break was taken.)

BY MR. KEMNA:

Q Doctor, are you familiar with an organization known as Council for Tobacco Research?

A I am aware that it exists. I know very little about the Council for Tobacco Research other

than there is some organization sponsored by tobacco companies that funds research projects.

Q Do you expect to express as part of any of your expert opinions any opinion that may relate to the organization, the activity or the direction of CTR, that is, Council for Tobacco Research, as a research-funding organization?

A No, sir, I know very little about the CTR.

Q Doctor, any other cancers than lung cancers that you can express an opinion within a reasonable degree of medical certainty are caused by cigarette smoking?

A In my opinion there is some causal relationship between cigarette smoking and development of bladder cancer. There is certainly a causal relationship between cigarette smoking and the development of head and neck cancers, cancers of the larynx, oral cavity, pharynx and esophagus. Those are probably the only cancers that I would offer an opinion that cigarette smoking causes.

Q Doctor, are you aware that all of these

cancers that you have just mentioned also have associated a number of other risk factors with their incidence?

A Yes, sir.

Q And let me do this in a summary fashion and see if this works to our benefit.

For cancer of the upper aerodigestive tract, would you agree that alcohol consumption and occupational exposures to asbestos, nickel, chromium, wood dust and sulphonic acid can be considered risk factors for the disease?

A I agree that alcohol consumption is a significant factor for the development of that disease. I have not previously expressed opinions as to whether or not asbestos is significant causally for those cancers, asbestos-related litigation, and I think it is a little unfair that I don't express that opinion at this time, either.

I honestly haven't reviewed the literature on nickel or cadmium for cancers of the head and neck region. I would have to look that data up before I

would comment.

Q Would you agree that dietary factors including deficiency of vitamin A or C, low carotene intake, high fat intake, low levels of vitamin E, low intake of fruits and vegetables, high coffee consumption, have all been associated with the occurrence of upper aerodigestive tract cancers?

A I am aware that a number of those factors have been looked at by various investigators, and I would not be surprised to find some of them have also found some associations. I myself would not express an opinion that any of those factors are significant causally in causing these cancers.

Q With respect to esophageal cancer, would you agree that Barrett's esophagus is a factor associated with the incidence of esophageal cancer?

A Yes, sir.

Q That would be considered a risk factor for esophageal cancer?

A Yes, sir.

Q Achalasia is a risk factor for esophageal

cancer?

A Yes, sir.

Q Radiation therapy is a risk factor for esophageal cancer?

A I believe I recall that it is, yes.

Q Alcohol consumption is a risk factor for esophageal cancer?

A Yes, sir.

Q Zinc deficiency is a risk factor for esophageal cancer?

A I was not aware of that, but I would not be surprised to hear of some reports that zinc deficiency is associated with esophageal cancer.

Q Malnutrition is a risk factor for esophageal cancer?

A Again, I am not aware of malnutrition being independently associated with esophageal cancer.

Q With respect to bladder cancer, is low intake of vitamin A a risk factor for the incidence of bladder cancer?

A I believe that there have been some reports

of that, yes, sir.

Q Are there certain occupational categories that would be considered risk factors for bladder cancer --

A Yes, sir.

Q -- including truck drivers, painters, auto workers, dry cleaners, chemical industry workers?

A I was certainly aware of the dry cleaners and chemical industry workers. I was unaware that truck drivers were at any increased risk for developing bladder cancer.

Q Are persons who work within a dye manufacturing facility at increased risk for bladder cancer?

A Yes, sir, that is well-described.

Q Are workers exposed to diesel or traffic fumes at an increased risk for development of bladder cancer?

A Yes, sir.

Q Doctor, are you familiar with a sputum cytology testing system known as Lung Check?

A No, sir, that sounds like a commercial name for some particular product or service.

Q Have you or any of your colleagues within your pathology department at Johns Hopkins been contacted by plaintiffs' counsel in association with class action litigation against the tobacco industry?

A No, sir. I am not aware of any of my colleagues having been contacted, and the only contact that I had with regard to tobacco litigation is that by Mr. Patrick's firm.

Q Have you collaborated with the Lung Cancer Institute Colorado in any development of early detection devices for lung cancer?

A There is an ongoing collaboration between Dr. Tokman at Johns Hopkins School of Public Health and investigators throughout the country including, I believe, in Colorado to attempt to identify lung cancer at an early stage through sputum cytology. In particular Dr. Tokman is hoping that immunochemical markers will improve the sensitivity for detection. He's also been working with other scientists in our

SPORE program, particularly Dr. Sidransky, to hopefully develop some molecular techniques that would be more sensitive for early detection of lung cancer.

Q Are there currently available any effective means of determining on an early detection basis those persons predisposed to development of lung cancer?

A Nothing has yet been established. An early detection study was done at several institutions, including Johns Hopkins, a number of years ago, and what was found was that even though some cases could be detected at perhaps an earlier stage, this did not result in improved long-term survival of the population in general.

Ultimately the test of these tests, in other words, what will determine whether or not these tests are important, is whether or not they can improve long-term survival, and that has not yet been demonstrated. I think it is a very worthwhile program, but there has not yet been a demonstration that it is successful and should be used programmatically for the general population.

Q Doctor, do you expect to express any opinions regarding the causation of nonmalignant diseases of the lung?

A I don't know. I think that really depends upon what Mr. Patrick or the firm requests of me.

Q Have you been asked at this point to express opinions on nonmalignant diseases of the lung?

A No, sir.

MR. PATRICK: Just with the exception of emphysema, which he mentioned earlier.

Q Do you expect to express an opinion with regard to the causation of cardiovascular disease?

A No, sir, I don't. That has not been discussed.

Q With respect to COPD, specifically now you are talking only emphysema?

A Yes.

Q Is emphysema the only condition that you will --

MR. PATRICK: As he stated earlier, the only real subject of his testimony or focus of his

testimony may be on the molecular basis of the causation of emphysema, the pathogenesis of emphysema on a molecular biological level, which I think he discussed before.

BY MR. KEMNA:

Q Would that be inclusive of any opinion with respect to whether or not cigarette smoking causes emphysema?

A Yes. I would say so, yes.

Q Is emphysema only caused by cigarette smoking in your view, Doctor?

A No, sir.

Q What other causes are there for emphysema?

A The only other significant cause of emphysema is a hereditary condition of a protease deficiency.

Q So to your --

A A protease inhibitor deficiency.

Q To the best of your knowledge, emphysema then would not occur if there was no cigarette smoking and if there was no genetic predisposition through

alpha-1-antitrypsin deficiency?

A The centriacinar type of emphysema that is what is commonly seen in cigarette smokers would not exist if there were no cigarette smoking or if there were no alpha-1-antitrypsin deficiency.

Q Have you observed in emphysema changes in the lungs of persons who have been examined at autopsy who were not smokers?

A Well, there are forms of emphysema which would include scar emphysemas or traction emphysemas associated with the scarring process. There is emphysema that spreads in interstitial spaces, even to the mediastinum or even up to the skin, but the pattern of emphysema that is characteristic of cigarette smoking I have never seen in an individual that has never smoked.

Q Is it true, Doctor, that you can identify emphysema in the lungs of individuals who are not smokers but were of an elderly age group?

A It is a different pattern of emphysema, a different type of emphysema.

Q So that if you were examining a death certificate and attempting to determine the etiology of emphysema and you had no other information but that emphysema was listed, you wouldn't have a basis for determining what the cause of the emphysema was; is that correct?

A If I were examining a death certificate and I saw emphysema listed, I would come to a conclusion that I believe is quite reasonable that they are referring to a form of emphysema caused by cigarette smoking.

Q That's absent any information regarding smoking history?

A Absent any other information, I think that I could conclude that it was caused by cigarette smoking and I would be right at least 90 percent of the time, perhaps a hundred percent of the time.

Q What proportion of individuals examined at autopsy in the age group of the 60s and the 70s would have some degree of emphysema present in their lungs?

A A significant percentage. Most such

patients have been cigarette smokers, and those that have not been cigarette smokers I am sure have had a significant cigarette exposure through their lifetime from the cigarette smoke.

Q Are you referring to environmental tobacco smoke?

A Environmental tobacco smoke, yes, that would be a significant, it can be a contribution. Again, most individuals that have any significant emphysema, and I think this is almost all individuals that have significant emphysema, seen at autopsy would have been cigarette smokers.

Q Doctor, with individuals who have the alpha-1-antitrypsin deficiency, what type of emphysema do they demonstrate?

A What we teach medical students is that they can have a panacinar emphysema as well as centriacinar emphysema. Often what we actually observe is a centriacinar emphysema that is not easily distinguished from cigarette smoking, but we can also observe a pattern of emphysema known as panacinar

emphysema that is different than what is seen in most smokers.

(A short break was taken.)

BY MR. KEMNA:

Q Doctor, do you have any knowledge of specific issues regarding the incidence of lung cancer in Mississippi?

A No, sir.

Q Do you have any specific information with respect to the incidence of nonlung cancers in the state of Mississippi?

A No, sir.

Q Have you made any attempt to determine any special issues that might relate to the environment in Mississippi that would possibly affect the incidence of lung cancer or other cancers in the state of Mississippi?

A No, sir. I really have not been requested to address issues specific for the state of Mississippi.

Q Are you familiar with an increased

incidence of lung cancer in the delta region of Mississippi?

A I am familiar that there is an increased incidence in cancers in what I thought was the delta region of Louisiana that possibly also extends up to Mississippi, along the Mississippi River.

Q Do you know what accounts for that increased incidence of cancer in that region?

A Well, it is probably multifactorial. There's a large chemical industry there. It's also my understanding that there is a very high incidence of cigarette smoking among that population.

Q Specific to the population within the delta region or specific to the population of the state that we are referring to?

A I don't know if it has been broken down by the delta region.

Q Do you know how --

A I don't know.

Q -- how the smoking behavior, that is, the prevalence of smoking in the state of Louisiana

compares to all the states in the United States?

A No, sir, I don't.

Q Do you know where it would rank?

A No, sir.

Q Do you know of any information about where the prevalence of smoking would rank for the state of Mississippi among all the states of the United States?

A My recollection is that it's one of the higher states for incidence of cigarette smoke.

Q From highest to lowest being a rank of 1 to 50, where would you put it?

A I don't know exactly. My recollection is that states -- among the higher smoking incidences -- include Maryland, West Virginia, Mississippi. I don't know exactly where these states rank.

Q You haven't made any independent study of the relationship or possible relationship between level or prevalence of smoking in the state of Mississippi and the incidence of lung cancer or other cancers in Mississippi, have you?

A No, sir, I have not.

MR. KEMNA: Let me make just a brief statement for the record.

According to our expectations, the notice for deposition submitted to Dr. Gabrielson through plaintiffs' counsel, we expected to have the production of the documents that he would have responsive to that request for production in advance of the deposition. Specifically those documents were to be produced by November 8th. We did not receive those documents and only today at the beginning of the deposition of Dr. Gabrielson did we receive the documents. We have not had an adequate opportunity to review the materials to do appropriate follow-up questioning of Dr. Gabrielson today.

We have also recognized that in the course of questioning that his opinions are broad. To the extent that we are unable to make the complete examination of Dr. Gabrielson on this one day that has been previously assigned for that purpose and in view of the limited description of the scope of Dr. Gabrielson's opinions as indicated by Deposition

Exhibit 2, I will reserve on the record the right to an additional day or days of deposition with Dr. Gabrielson sufficient to complete appropriate examination of the broad subject areas of his apparent expected testimony, and in fact there appears to be a good deal of uncertainty at this point as to the exact scope of his opinions expected to be given at trial.

Finally, my basis for reserving this additional day or days of deposition is based upon the requirements within Mississippi Rules of Civil Procedure as we were entitled to an advance description of Dr. Gabrielson's testimony through the scheduling order for discovery in this case. Specifically we are entitled to the disclosures under Rule 26 A 4, subpart A, small case I, and that is, the statement should have included the subject matter on which the expert is expected to testify and to state the substance of the facts and opinions to which the expert is expected to testify and a summary of the grounds for each opinion. This report does not provide any substance anywhere close to the breadth

and detail of the opinions that Dr. Gabrielson has described here at the deposition today and that he would expect to provide testimony at the time of trial. Therefore it is not in compliance in my estimation of Rule 26, and that completes the deposition.

MR. PATRICK: Okay.

Madam Court Reporter, if you would just note for the record the ending time of the deposition as well as the beginning time for the record.

THE REPORTER: Are you getting a copy?

MR. PATRICK: Yes.

THE REPORTER: Do you have a reading requirement?

MR. PATRICK: I believe in this instance the doctor should read and sign the deposition.

(Thereupon at 5:40 p.m. the deposition was concluded.)

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State of Maryland

City of Baltimore, to wit:

I, DEBORAH K. WILKINS, a Notary Public of the State of Maryland, City of Baltimore, do hereby certify that the within-named witness personally appeared before me at the time and place herein set out, and after having been duly sworn by me, according to law, was examined by counsel.

I further certify that the examination was recorded stenographically by me and this transcript is a true record of the proceedings.

I further certify that I am not of counsel to any of the parties, nor in any way interested in the outcome of this action.

As witness my hand and notarial seal this 5th day of December, 1996.

Deborah K. Wilkins, RPR

Notary Public

My commission expires: 6/1/99

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Deposition of Edward Gabrielson, M.D.

November 15, 1996

CERTIFICATE OF DEPONENT

I hereby certify that I have read and examined the foregoing transcript, and the same is a true and accurate record of the testimony given by me.

Any additions or corrections that I feel are necessary, I will attach on a separate sheet of paper to the original transcript.

Edward Gabrielson, M.D.